

Leo Sher, Joav Merrick (Eds.)
Adolescent Psychiatry

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Edited by
Joav Merrick

Greydanus DE, Patel DR, Omar HA, Feucht C, Merrick J, eds.

Adolescent Medicine: Pharmacotherapeutics in General, Mental and Sexual Health.

Berlin: De Gruyter, 2012.

ISBN 978-3-11-025522-5

e-ISBN 978-3-11-025570

Greydanus DE, Patel DR, Omar HA, Feucht C, Merrick J, eds.

Adolescent Medicine: Pharmacotherapeutics in Medical Disorders.

Berlin: De Gruyter, 2012.

ISBN 978-3-11-027580-3

e-ISBN 978-3-11-027636-7

Tareen RS, Greydanus DE, Jafferany M, Patel DR, Merrick J, eds.

Pediatric Psychodermatology: A Clinical Manual of Child and

Adolescent Psychocutaneous Disorders.

Berlin: De Gruyter, 2012.

ISBN 978-3-11-027387-8

e-ISBN 978-3-11-027393-9

Adolescent Psychiatry

A Contemporary Perspective for Health Professionals

Edited by
Leo Sher and Joav Merrick

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ISBN 978-3-11-031656-8
e-ISBN 978-3-11-031661-2
Set-ISBN 978-3-11-031662-9

Library of Congress Cataloging-in-Publication data

A CIP catalog record for this book has been applied for at the Library of Congress.

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at <http://dnb.dnb.de>.

© 2013 Walter de Gruyter GmbH, Berlin/Boston

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Typesetting: Compuscript Ltd., Shannon, Ireland
Printing and binding: Hubert & Co. GmbH & Co. KG, Göttingen
Cover image: iStockphoto/Thinkstock
∞ Printed on acid-free paper
Printed in Germany
www.degruyter.com

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Introduction

Education of health professionals about adolescent psychiatry

Leo Sher and Joav Merrick

Psychiatric disorders in adolescents are an important social problem which is relevant to almost all health care professionals (1–3). According to the results of The National Comorbidity Survey–Adolescent Supplement (NCS-A), the lifetime prevalence of anxiety, behavior, mood, and substance use disorders among adolescents was 31.9%, 19.1%, 14.3%, and 11.4%, respectively (1). Approximately 40% of participants in this survey with one class of disorder also met criteria for another class of lifetime disorder. Comorbidity is increasingly recognized as a key feature of mental disorders among adolescents. Female adolescents are more likely than males to have mood and anxiety disorders, but less likely to have behavioral and substance use disorders (1, 3).

Regretfully, medical professionals are not sufficiently trained about adolescent psychiatric disorders. For example, primary care providers correctly identify less than a fourth of youth with a depressive or anxiety disorder (3). Also, many clinicians underestimate the importance of the problem of adolescent psychiatric illnesses and suicidal behavior (4). Lack of skilled medical providers impedes the delivery of needed services to adolescents with mental health issues. This coupled with a lag in the ability of primary health care services to incorporate psychiatric interventions, and a failure of public health initiatives to pay attention to adolescent mental health problems has led to continuing gaps in care over decades despite the public pronouncements of needs.

Educating health care providers and trainees about the signs and symptoms of adolescent mental disorders and providing them with tools to recognize, evaluate, and manage these disorders are a very important task. The high prevalence, morbidity, mortality, accessibility, and treatment responsiveness of many adolescent psychiatric issues make them a good and important target of care.

Adolescents of today are born into families and communities that differ in regard to ethnicity, culture, language, religion, environment and the opportunity to benefit from education and wealth. They are exposed to revolutionary new technology. Teenagers have exciting, rapidly changing lives of promise. Most adolescent patients, especially in today's age of fragmented families and communities, value the chance to connect with an educated and responsible adult. Therefore, all medical providers may contribute a lot to the mental health care of adolescents.

One of the greatest documents in the history of the humankind, The Declaration of Independence of the United States of America pronounces that “We hold these truths to be self-evident, that all men are created equal, that they are endowed by their Creator with certain unalienable rights, that among these are life, liberty and the pursuit of happiness” (5). We believe that adolescents all over the world have rights

that are inherent and inalienable, reflective of adolescents being full members of the human society. The mental health of adolescents is essential for sustaining healthy and productive societies.

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Section I: **Neurobiological aspects**

1 Adolescents with psychiatric disorders: brain structural and functional changes

José Javier Miguel-Hidalgo

During adolescence hormonal and neurodevelopmental changes geared to ensure reproduction and achieve independence are very likely mediated by growth of neural processes, remodeling of synaptic connections, increased myelination in cortical prefrontal areas, and maturation of connecting subcortical regions. These processes, greatly accelerated in adolescence, follow an asynchronous pattern in different brain areas. Neuroimaging research using functional and structural magnetic resonance imaging has produced most of the insights regarding brain structural and functional neuropathology in adolescent psychiatric disorders. In schizophrenia, first episodes during adolescence are linked to greater-than-normal losses in gray matter density and white matter integrity, and show a divergence of maturational trajectories from normative neural development, in a progression similar to that of adult-onset schizophrenia. Anxiety and mood disorders in adolescence have been linked to abnormally increased activity in the amygdala and ventral prefrontal cortical areas, although some data suggest that neural abnormalities in the amygdala and anxiety maybe particularly more frequent in adolescents than in adults. Alcohol misuse in adolescence results in reduced integrity in the white matter and reduced gray matter density that, given the high intensity of adolescent synaptic and myelin remodeling, may result in persistent and profound changes in circuits supporting memory, emotional and appetitive control. Interaction of persistent changes due to prenatal exposure with contemporaneous expression of genetic factors and disturbing environmental exposure may be an important factor in the appearance of psychiatric disorders in adolescence. Further progress in understanding adolescent psychopathology will require postmortem research of molecular and cellular determinants in the adolescent brain.

1.1 Introduction

Adolescence is a period in which the need for establishing new social and personal relationships, and reaching independence and reproductive success is supported by dramatic hormonal, neural and behavioral changes. Similar to other developmental dynamic processes, changes in brain circuits during adolescence are an integral part of genetically programmed developmental processes. At the same time, those processes allow ample room for plastic changes to adapt to the social and natural environment. The ideal result of those processes is an emotionally balanced young adult. However, the unraveling of the developmental programs and the rapid neuroplastic changes during adolescence (when exposed to negative factors or influenced by inheritable or epigenetic deficits) are susceptible to the formation of faulty brain circuits that

manifest themselves as psychiatric or neurological disorders. In fact, first episodes for many of the main psychiatric disorders later diagnosed in adults occur during adolescence or close to the end of adolescence or may depend of alterations primed in adolescence. Determining which features of morphology and brain activity in adolescents represent a pathological change when compared to adult brains requires, however, an understanding of characteristics of the normal, non-psychiatric adolescent brain as compared to the brain of maladapted psychiatrically adolescent individual.

While psychological and social aspects of psychiatric disorders have been extensively researched since very early in adolescent psychiatry studies, specific neuropathological, neurological or physiological studies of brain areas involved in adolescent psychopathology is more recent. In the present review we present first a summary of cellular, neuroanatomical and neuroimaging characteristics that differentiate the normal adolescent brain from the adults as well as those features that signal a transition towards the establishing of adult structure and connectivity. Then we will review studies that report the localization of structural and functional neuropathological changes to specific brain areas in schizophrenia, anxiety, depression and substance abuse disorders in adolescents as revealed by neuroimaging techniques. This reporting will be followed by a consideration of the influence of relevant genetic variants on localized neural activity in the brain of adolescents with schizophrenia, anxiety and mood disorders.

During adolescence changing levels of cognitive abilities, impulse control, language and motor coordination show great plasticity to allow for the transition to mature behavior and cognition. Insofar as the same systems that must display this plasticity are affected by disturbances during prenatal and postnatal life, adolescence could be particularly vulnerable to neuropathological alterations that result in psychopathology. So far, the majority of studies on structural or functional brain changes in adolescents with psychiatric disorders have been based on magnetic resonance imaging (MRI) (1, 2). Brain structural MRI is based on the differential behavior of protons of water molecules in gray and white matter when exposed to a variable magnetic field. The contrast between structures varying in the response to magnetic field alterations allows delineating local groupings of neurons and fibers and determining their size in absolute and relative terms. Computer software specially designed to assess morphometric parameters of MRI-discriminated brain components allows to measure cortical gray matter thickness, density of gray and white matter, volume of subcortical structures, cortical surface, size and shape of cortical gyri and sulci as well as brain growth.

Diffusion tensor imaging (DTI) is an application of structural MRI to the measurement of the diffusion of water molecules. Within a magnetic field these molecules tend to align into preferential directions according to their ability to diffuse across or along the arrangement of biological structures that surround them. If diffusion and alignment occur in many directions, a measurement of high fractional anisotropy is made. If, on the contrary, diffusion of water molecules is restricted to specific directions,

(for example in white matter along myelinated fiber bundles) then fractional anisotropy is reduced, which is interpreted as sign of greater integrity and maturity of the axons involved (3). Functional magnetic resonance imaging takes advantage of the differential magnetic properties of oxygenated versus deoxygenated hemoglobin in the brain blood circulation to determine blood oxygenation level-dependent contrast signal (BOLD signal) (4). Blood oxygenation changes caused by fluctuations in blood flow and oxygen extraction are considered to closely reflect neural activity, because there is a tight coupling between increases in local neuronal activity and required increases in blood flow to support augmented metabolic demand from neurons (5). All the structural and functional variables mentioned above experience significant changes in various brain regions during adolescence, making neuroimaging studies particularly appropriate to defining them.

Earlier studies that revealed developmental changes at the microscopic level in gray and white matter in the adolescent brain were mainly based on histological examination of the postmortem brain (6–8). However, most of what is known on brain development at the cellular and molecular level in adolescents derives from studies in experimental animals, and there is no direct information as yet on the cellular and molecular neuropathology of the human adolescent brain in psychiatric disorders. Consequently, in this review we discuss knowledge on the neuropathological alterations in adolescents with major psychiatric disorders mainly as they have been revealed in structural and functional MRI studies, although evidence from other approaches is introduced when appropriate. The resolution of images in MRI-based neuroimaging research, although improving, is still insufficient for research at the cellular level. However, MRI neuroimaging studies present several distinct advantages: they do not involve the use of potentially deleterious ionizing radiation and thus can be used more than once in living subjects; unlike postmortem neuroanatomical studies, it is practical to include many subjects in a single study, thus increasing statistical power; longitudinal studies are possible to determine developmental trajectories and effects of environmental changes (2). Thus, unless otherwise specified, research results discussed throughout this review will correspond to MRI-based studies.

1.2 Neuroanatomical and functional changes in the normal adolescent brain

In the early postnatal years the brain experiences an exponential increase in the numbers of synapses, dendritic and axonal branches and myelination that result in dramatic increases of brain size (9, 10). Later in childhood there is a stabilization of brain size and the number of synapses, although myelination continues to expand into several brain areas, and white matter connecting the prefrontal cortex to other brain regions appears to increase. In fact, during adolescence the volume of frontal gray matter as visualized by structural MRI has been described to decrease while white

matter steadily increases (11). The process of synaptic change, however, retakes vigorously at the beginning of adolescence and for most of its duration, with initial overproduction and later elimination of some synapses, resulting so-called synaptic pruning in the prefrontal cortex and other cortical areas (7, 12–14). Myelination progresses further also in the prefrontal cortex (6), and in other regions highly relevant to development of psychiatric disorders (15). Synaptic changes consist in a reduction of synaptic density that is likely reflected in a concomitant reduction in the volume of gray matter in the prefrontal cortex and the striatum, although volume reductions may not be entirely accounted for by synaptic changes (16), and in some structures such as the amygdala, the hippocampus and the posterior temporal cortex there is an increase of gray matter density during adolescence (1, 17, 18). The possibility that neuronal loss also contributes to gray matter size changes or synaptic pruning in specific cortical areas cannot be ruled out because Markham et al (19) have found decreases in neuronal numbers in the ventral prefrontal cortex of adolescent rats. Despite the overall pattern of synaptic pruning, specific axonal pathways connecting the prefrontal cortex and the amygdala experience further grow and branching, and result in increased white matter volume during adolescence. As discussed by Sowell et al (1) some reductions of gray matter density, which are paralleled by increases in white matter volume, and the apparent thinning of the gray matter measured by MRI-based mapping methods, might result from changes in myelination at the border between gray and white matter and not just be a consequence of synaptic pruning. On the other hand, measurement of brain growth at the surface of the cerebral cortex reveals that, despite the reduction of gray matter density, there is growth at the cortical surface of specific brain regions between adolescence and adulthood, particularly in the dorsal aspects of the frontal lobes and the left orbitofrontal cortex (1). In addition, the primary language cortex in the perisylvian region sets itself apart because thickness and density of the gray matter increase during adolescence and into early adulthood (11, 20, 21). Thus, there is a high degree of regional specificity and non-linear occurrence of structural and functional changes in the adolescent gray and white matter that attest to specific changes geared to adaptations for acquisition of relative independence and the ability to reproduce. Brain imaging techniques support that, in all, the various maturational processes taking place in the adolescent brain result in an increasing regulatory role by the prefrontal cortex (22).

A recent DTI study in children, adolescents and adults, showed that measures of radial diffusivity (which diminishes as fiber bundles mature) decrease in particular but broadly distributed pathways connecting cortex and brain stem nuclei in adolescents, indicating an increase in the integrity of axon bundles and myelin maturation. However, other pathways supporting prefrontal-striatal and inter hemispheric connections do not fully mature until adulthood (3). It is also important to note that new studies have found that an increase in white matter is largely dependent on hormonal changes and this hormonal influence very likely also affects the microstructure of fiber bundles in the gray matter (23). The dependence on hormonal changes and the difference in specific hormonal changes between males and females may underpin

distinct microstructural development of white matter tracts in adolescent in males and females and clearly deserves further studies.

1.3 Models of brain functional changes in adolescents with psychiatric disorders

Some behavioral features that in average appear to be concentrated in the adolescence years may be related to an adolescent pattern of brain activity that is not found during normal childhood or normal adulthood. Thus, absence of this pattern in adolescent subjects might be a sign of psychopathology and be associated to maladaptive behaviors. On the other hand an exacerbation of, rather than a departure from, that pattern in comparison to normal adolescents might result in psychopathology as well. In other cases, structural and functional alterations in adolescents maybe similar to those observed in adults affected by the same disorders. This distinction between adolescent-specific and adult-like changes is important because therapeutic interventions effective in adults maybe be amenable to the treatment of adolescents in some cases while, in others, interventions might be required to be also adolescent-specific. The distinction also applies to psychiatric or personality disorders that, being described in adolescence and childhood, may be either associated with structural alterations that are different in children and adolescents, or respond to the same type of cerebral alterations. For example, while a distinction is made between early-onset and adolescent-onset conduct disorder, regionally specific reductions of gray matter in the amygdala and insular cortex are common to both early- and adolescent-onset conduct disorder (24).

Neuroimaging studies show that the neural activity in various prefrontal regions of normal adolescents is increased or decreased during particular cognitive and emotional tasks as compared to adults and that the relatively altered function is associated with emotional and cognitive responses reflecting more impulsivity, and greater risk-taking by adolescents. Since these are normal features of adolescence, there is a legitimate question of whether pathological behavior or emotions in adolescents correspond to just an exacerbation of normal adolescence function or if functional brain changes take onto a pattern that differs both from adults and from normal adolescents. A model has been put forward to explain emotional, cognitive and behavioral features of adolescence as they differ from adults in terms of brain functional changes (25). This model proposes the existence of three brain functional nodes representing different levels for the processing of stimuli, and the establishment of motivations, decisions and plan making: the detection node (some occipital and temporal areas), the affective node (amygdala, hippocampus, ventral striatum and orbitofrontal cortex) and the cognitive-regulatory node (other prefrontal areas). Plasticity and rearrangements in the connectivity within and between these nodes would form the basis for the emotional and behavioral changes observed during

adolescence, and provide a substrate for alterations that can lead to the first time appearance of psychiatric disorders (25–27).

The above three-node model stresses the importance of connections between the nodes for the development of social interactions during adolescence. In fact, recent longitudinal studies on the responsiveness of relevant cerebral regions of adolescents to facial affective displays have shown distinctive changes in BOLD fMRI signals in early adolescence as compared to late childhood (28). In adolescents, the activity in the ventromedial prefrontal cortex and the ventral striatum was significantly enhanced in response to affective facial displays, while in the amygdala, although the displays caused an increase in BOLD signal, this was not increased as compared to late childhood (28). Most interestingly, a higher response in the ventral striatum has been related to higher positive affect and fewer depressive symptoms in adolescents (29, 30). Since the role of other prefrontal regions in emotional regulation appears not to be fully developed until late in adolescence or early adulthood, pathological alterations in the ventral striatum of ventromedial prefrontal cortex might have to be taken into account when establishing the pathophysiology of affective disorders in adolescents to eventually ascertain the role, if any, of these alterations in adult psychopathology. Prenatal alcohol exposure also results in specific effects on brain structure when examined in young adults (31). Although this study was not done strictly in adolescents one of the main conclusions is that overall and localized reductions in brain size and IQ scores associated to prenatal alcohol exposure are not directly related to general physical development in the young adult but to head development and gestational factors (31), which could fully show their influence during adolescence and early adulthood. In adolescents, activity in brain areas involved in the development of cognition and language are also affected by the length of pregnancy (pre term versus full term birth), so that pre term birth is associated with higher activity of the medial frontal gyrus when adolescents are confronted with syntactic difficulty in a task of sentence comprehension (32). The significance of these changes is, however, unclear, since formal test scores indicate no differences in scholar achievement between pre term and full term adolescents (32).

As explained by Sturman and Moghadam (25) another triadic node model of brain circuits that would underlie psychiatric alterations in adolescence puts the emphasis on the balance between affective processing and cognitive control, which might explain risk-taking behaviors in adolescence. The nodes in this model include the ventral striatum (reward approach), the amygdala (punishment avoidance) and the prefrontal cortex (modulation node). The balance between the reward approach and punishment avoidance would be controlled by the prefrontal cortex. Underdevelopment of the prefrontal cortex in adolescents as compared to adults would make it difficult to control a predominance of the reward-approach node in detriment of the punishment-avoidance node and thus would generate heightened risk-taking behavior. Recently, it has been observed that in the case of substance abuse a significant link exist between lower than normal activity and reduced density of gray matter in the ventral striatum and higher risk taking in adolescents with potentially

problematic substance problems (33), further supporting the suggestion that an adequate level of activity in the ventral striatum during adolescence is crucial for various aspects of emotional and behavioral control, particularly at a time when prefrontal circuits are still far from having achieved mature development. Disruption of circuits served by the ventral striatum then could contribute to the appearance of psychiatric problems during adolescence.

Despite the suspected implication of frontal brain plastic changes in the increase of risk taking behavior during adolescence there is recent evidence that type of behavior might be related to an accelerated maturation of particular circuits. Using DTI, Berns et al (34) found that engagement in dangerous activities in adolescence was positively correlated with fractional anisotropy, and negatively correlated with transverse diffusivity in frontal white matter tracts, which was interpreted as increased myelination or increase in the density of fibers, both considered signs of maturation. Thus, particular caution must be exercised in interpreting how behavioral, functional and structural maturation interact with behavior during adolescence to eventually achieve a pattern of adult-like behavior. Only the eventual maturation of the prefrontal cortex would result in the fully developed, adult pattern of emotional control and behavior. In both models outlined above the role of a balanced influence of the brain nodes and the modulating role of the prefrontal cortex are paramount and offer opportunities to formulate hypotheses and test them experimentally.

1.4 Structural and functional changes in schizophrenia

In adolescents and children diagnosed with schizophrenia, structural MRI studies have shown a significantly lower volume of total cortical gray matter and superior frontal gyrus gray matter, suggesting that structural and functional pathology might precede the manifestation of schizophrenia in late childhood and adolescence (35). In addition, longitudinal studies in adolescents at very high risk for developing schizophrenia show that abnormal structural changes in gray and white matter during adolescence are critical for the transition to psychosis in adolescents. In subjects at very high risk for schizophrenia there is a marked reduction of the increase in white matter seen in control adolescent subjects, while the shrinkage in the gray matter of the left middle temporal gyrus is significantly greater than in controls or subjects with high risk who do not develop psychosis (36). Since maturity of white matter tracts is seen as a sign of increasing control by prefrontal cortical and association areas it is possible that a reduced maturation of the corresponding connecting pathways during adolescence is a critical anomaly leading to psychosis. Studies on the developmental progression during adolescence of gray and white matter abnormalities in adolescent-onset schizophrenia, as compared to adult-onset schizophrenia, show a greater pathology in the adolescent-onset condition (37). In addition, as compared to gray and white matter development in non-psychiatric subjects, a longitudinal examination revealed that the

development of gray and white matter in adolescent schizophrenia is delayed from adolescent controls and progressively diverges from normal control subjects to follow a similar pattern to the abnormal progression of neuropathology in adult-onset schizophrenia (37). The progressive divergence from the normal developmental pattern in adolescent-onset schizophrenia would be in agreement with a study in which examination of gray and white matter structure in ultra high risk adolescent subjects (but not yet diseased) did not reveal significant differences from adolescents not at risk (38), suggesting that the appearance of psychotic symptoms is tightly linked to the development of detectable structural alterations and only upon manifestation of the disorder there is development of brain structural anomalies (36).

In addition to a role for detectable neuropathological alterations in cortical gray matter and the underlying white matter in adolescent schizophrenia, there is a model that stresses the role of pubertal and postpubertal changes in the HPA axis and hippocampus as important contributors to the expression of vulnerability for psychosis in adolescents (39–41). According to this model, a developmental or genetically determined vulnerability to psychosis might find expression during adolescence because there are dramatic hormonal and neural changes in the HPA-hippocampus link that, combined with heightened chance for stress responses, result in unraveling of the vulnerability. Stress responses result in the release of corticosteroids that, beside actions on various cell types across the body, exert an important modulatory role on mineralocorticoid and glucocorticoid receptors (MR and GR). These receptors are very abundant in the hippocampus and modulate responses of hippocampal cells. Sustained increases in corticosteroids, however, can be toxic to hippocampal neurons, and in fact in normal subjects or in subjects with pathologically high cortisol levels there is a significant inverse correlation between cortisol levels and hippocampal volume (42–46). In first-episode, non-medicated subjects with schizophrenia there is elevated levels of basal cortisol (47) and there is also evidence for smaller hippocampal sizes than in non-psychiatric control subjects (48). One study specifically targeted changes in whole brain and hippocampal volumes, showing that whole brain volume was significantly smaller in subjects with schizophrenia, but that the difference in hippocampal volume was not statistically significant. However, both duration of illness and severity of psychopathology were negatively correlated with hippocampal volume (49). More recent studies in adolescents with early onset schizophrenia further support marked structural deficits early in the disorder, showing a significant thinning of the gray matter bilaterally in both gyri and sulci of the superior frontal gyrus and in dorsal, ventral and medial locations within the prefrontal cortex (50). These data together with the first-episode findings suggest that adolescence maybe a critical period when the fast progression and manifestation of schizophrenia result in immediate structural changes or these changes, upon appearing, immediately manifest as psychotic symptoms. More recently, DTI, which examines the integrity of fiber bundles connecting brain areas, has further shown that there is a reduction in connectivity in children and adolescents with schizophrenia as reflected by a

decreased fractional anisotropy and increased average diffusivity (51). These results point to the possibility that a dysfunctional link between the HPA and hippocampus contributes to the first manifestations of schizophrenia.

Higher stress sensitivity during adolescence is proposed to be an important link between environmental influences and the manifestation of psychiatric disorders, particularly psychosis (39). Prolonged exposure to stress would alter the HPA-hippocampus reciprocal modulation to result in alterations increasing the risk for psychosis. While in normative adolescence there is the expectation of continued increase in hippocampal volume (52, 53), increased stress sensitivity may, in some predisposed individuals, result in reduced hippocampal volume as suggested by a smaller hippocampus in animals exposed to prolonged stress after the onset of puberty (54).

1.5 Neuroimaging in adolescents with anxiety disorders

While schizophrenia and depression are described in childhood, most first episodes of these disorders occur mainly in late adolescence and early adulthood (39). Moreover, for schizophrenia diagnosed in early adulthood, progressive deterioration of function can be already detected early in adolescence (55). This temporal pattern does not necessarily apply to all psychiatric disorders. For instance, anxiety disorders are highly prevalent in childhood and adolescence (56). Although anxiety is frequent in the course of childhood, it seems to resolve by late adolescence in most cases, but if anxiety persists during adolescence there is an increased probability for anxiety taking a chronic course in the adult. Thus, chronicity in the adult may result from the inability to resolve during adolescence a disorder that is highly prevalent in adolescence and childhood. The development and refinement of attentional processes during adolescence has been proposed as a substrate for pathological enhancement of anxiety processes in adolescence and into adulthood (56). Since circuits and brain responses underlying attention have been relatively well identified and characterized, functional MRI has been used to determine brain centers that may be altered during attentional tasks with emotional components. For instance, when subjects are presented with angry faces, fMRI studies are showing increased activity in the ventrolateral PFC of adolescents with generalized anxiety disorder (GAD) as compared to non-anxious adolescents (57). Likewise, adolescents with GAD show greater activation of the amygdala to fearful faces than healthy controls, although greater response is only evident when the subjects are instructed to focus their attention on their own subjective evaluation of fear, and not when viewing faces without specific instructions (58), consistent with previous studies that found increased activation of the amygdala in adolescents and children with anxiety and depression (59). Other regions of the prefrontal cortex such as the ventromedial orbitofrontal cortex have been found to display abnormally low activity in tests for fear sensitivity, which has led to the proposal that a misbalance between limbic regions highly sensitive to the drastic

hormonal changes of adolescence, and prefrontal regions responsible of cognitive control would greatly contribute to the development of psychopathology during adolescence (60). This proposal also implies that, in the normally developing brain, hormonally driven high activation in reward and limbic systems must be progressively controlled by the more linearly developing cognitive influence of the prefrontal cortex. Prolongation of the period between hormone-related limbic activation and progressive cognitive control would result in increased risk for manifestations of psychopathology in adolescents and young adults (60).

1.6 Neuropathology in adolescents with depression

In adolescence, major depressive disorder (MDD) and bipolar disorder (BD) share an increased activation of the amygdala with anxiety disorders (61). This greater amygdalar activation appears to extend to healthy children and adolescents at high risk for depression (as compared to non-high-risk children) when presented with fearful faces (62). In addition, some studies describe a decrease in the volume of the amygdala of adolescents with depression, although, intriguingly, the ratio of the amygdala volume to hippocampal volume is increased in adolescents with depression (63). The hippocampus itself has been the focus of neuroimaging research. In one study researchers found a decrease in hippocampal volume in adolescent depression, a finding similar to that in adult recurrent depression (64). However, another study with subjects in early adolescence did not detect a significant difference between subjects with depression and healthy subjects (61), suggesting that progression of depression during adolescence might result in hippocampal volume reduction. Unlike studies in adults, fMRI studies in adolescents with bipolar depression did not find altered activation of prefrontal areas (although there was absence of the correlation of activation with age observed in controls), but noted an increase in activation of thalamic and striatal structures when adolescents were subjected to a cognitive color naming Stroop task (known to involve prefrontal circuits) (65). At a difference with decreased gray matter volume of the subgenual prefrontal of adults with MDD and BD, the same region in adolescents with BD is not changed as compared to healthy controls. Nonetheless, the volumes of gray and white matter of the prefrontal cortex of adolescents with MDD are significantly changed as compared to controls, with larger volume in the gray matter and smaller volume in the white matter (66). Application of DTI to the adolescent brain has also shown that integrity of white matter fibers is affected, showing decreased fractional anisotropy in fiber tracts that originate from the subgenual anterior cingulate cortex and involve frontolimbic connecting pathways (67). Since during normal adolescence there is a progressive increase in white matter volume and a reduction in the volume of gray matter, it seems that there is a defect in the maturation of brain pathways in adolescents with depression. Whether this defect is a cause for or an effect of depression remains to be fully elucidated. Functional consequences of

suspected altered connections in the adolescent brain with depression have been more recently examined in resting state fMRI. This approach has shown that connectivity between several prefrontal cortical areas, superior temporal gyrus and the insular cortex is significantly reduced (68), while connectivity with between the amygdala of various prefrontal regions appears to be enhanced (69).

Postmortem neuropathological and molecular studies of the human brain in psychiatric disorders during adolescence are understandably scarce with the only exception of suicide. Suicide is an important cause of death during teenage years (70) and in many cases is associated with psychiatric disorders. Studies on postmortem brain of suicide adolescents have reported an increase in binding and mRNA for 5-HT_{2a} serotonin receptors, which, in the case of binding, is also observed in adult suicide (71). Also in teenage suicide victims a postmortem study found that brain derived neurotrophic factor (BDNF) and its receptor, TrkB, were significantly reduced in the prefrontal cortex and hippocampus (72). CREB (protein and mRNA) a transcription factor that participates in the transcription of BDNF mRNA was also lower in the prefrontal cortex of adolescent suicides as compared to controls subjects (73). Given the involvement of BDNF in synaptic plasticity and neurite growth, reduced BDNF in critical brain areas may result in reduced plasticity in the brain of suicide victims, which may contribute to psychopathology leading to suicide. Increased proinflammatory cytokine expression has been described in the postmortem brain of MDD and proposed to contribute to the pathophysiology of depression. Recent studies in brains from teenage suicides have found that there is an increase in the levels of TNF-alpha and IL-beta as compared to controls (74), raising the possibility that neuroimmune alterations are also part of the pathological processes underlying depression in adolescents.

1.7 Neuropathology in the adolescent brain and substances of abuse

Due to their great medical and social importance the neuropathological effects of alcohol intake during adolescence have received increasing attention. Binge and sustained alcohol drinking have been shown to cause effects in adolescents that differ significantly from the effects in adults, although the direction of many of those changes is similar (75). In adolescents, alcohol drinking results in a reduction of the volume of the hippocampus and prefrontal cortex and the reduction is positively correlated with the duration of alcohol abuse (76–78). Moreover, in binge-drinking adolescents not under medical treatment there is a significant and widespread decrease in the integrity of the white matter as studied by DTI (79). These structural abnormalities in adolescents are very likely accompanied by physiological and molecular changes in brain regions and processes heavily involved in emotional and cognitive regulation of behaviors related to substance abuse. For instance, alcohol abuse in human adolescents and in animal models causes larger memory impairments than in adults (80–83). Correspondingly,

some studies in rats show that binge-drinking causes larger neuronal damage in the frontal cortex of adolescent than adult rats (84, 85), while other studies demonstrated greater inhibition of NMDA-based synaptic activity in the adolescent hippocampus and cingulate cortex, and a greater inhibition of long term potentiation (LTP) (86), which is considered a basic neurophysiologic mechanism involved in learning and memory. Some of the damage and long-term behavioral effects caused by alcohol during adolescence would involve significant alterations in dopaminergic and glutamatergic pathways of frontocortical and striatal brain centers, which could be mediated by epigenetic changes in histone acetylation (87). Knowledge of these changes may open the door to designing treatments of alcohol-related disorders in adolescence based on the inhibition of histone deacetylases (88).

The involvement of addiction or exposure to cocaine in pathological brain changes during adolescence has been also studied with neuroimaging methods. For instance, prenatal exposure to cocaine has been found to result in changes of connectivity as determined by DTI (89), which shows that at least 10 different landmarks in several fiber tracts of white matter are different between adolescents exposed to prenatal cocaine and non-exposed controls. It is important to determine these changes because adolescents prenatally exposed to cocaine show deficits in intelligence, executive function and language skills which greatly depend on the systems affected by prenatal cocaine exposure (89). In turn, binge-like cocaine exposure during adolescence in experimental rats results in gene expression changes that involve chromatin remodeling (indicating persistent changes) in the prefrontal cortex in adulthood (90). Thus, in adolescence there could be expression of pathological alterations as a consequence of prenatal exposure to cocaine or other brain altering agents while the brain is still susceptible to lasting changes due to adolescent drug abuse, raising the possibility of a compounded or synergistic damaging interaction between acute exposure in adolescence and the consequences of past unwanted exposures. As in the case of adolescent exposure to alcohol, long-term consequences of cocaine abuse during adolescence may involve epigenetic changes as illustrated by reduced methylation of histone 3 in adolescent rats administered cocaine (90).

1.8 Gene variants and functional neuroimaging

Recent studies have started to consider the contribution of relevant gene variants to the emergence or presence of anxiety and mood disorders in adolescents and their functional consequences in specific brain areas. Variants of the gene for the serotonin transporter (5-HTT) have been shown to modulate the manifestation of symptoms of anxiety and depression, with subjects (psychiatric and non-psychiatric) carrying the S and L(g) alleles more prone to anxiety and depression symptoms (91) and to higher activation of the amygdala measured by fMRI when looking to fearful faces in a fear-detecting mode than subjects with two L(a) alleles (92). In adolescents,

follow-up studies have further shown that in a fear monitoring situation fearful faces also cause higher amygdala activation in S and L(g) carriers but only when the patients are non-psychiatric (93). Surprisingly, adolescent subjects with psychiatric diagnosis had higher amygdala activation when they carried two L(a) alleles, an effect opposite to the one observed in adults. This peculiarity of allelic effects in adolescents may reflect a vulnerability of the asynchronous development pattern of various cortical and subcortical centers in adolescent subjects or a lack of experiences that eventually may result in greater effects of S/L(g) alleles (93) only in adults.

Allelic variants of brain-derived neurotrophic factor (BDNF), with probable effects on the activity of BDNF as a trophic factor, might be linked to depression and anxiety in adults (94, 95). To assess whether those gene variants also influenced psychiatric diagnosis in adolescents, Lau et al (77) studied MRI-detected activity in brain regions that are activated when viewing faces with different emotional loads (fear, happiness, indifferent). It was found (96) that adolescents diagnosed with anxiety or depression had higher activation in amygdala and hippocampus in response to fearful faces than non-psychiatric controls, and that this activation was significantly higher in psychiatric adolescent subjects that carried the Met66 allele (as opposed to Val/Val homozygote carriers), suggesting that localized brain functional effects of genetically-based changes in the sequence and activity of BDNF are already detectable by fMRI in adolescence.

1.9 Conclusions

During adolescence dramatic changes in behavior, bodily growth, and in cognitive and emotional control are concomitant with significant morphological and functional changes in brain areas implicated in the pathophysiology of psychiatric disorders. In some individuals, this maturational transition is associated with the first manifestations of major psychiatric disorders during or shortly after the adolescent period. At different times during adolescence various processes of neural remodeling and growth take place at different locations within the frontal cortex and connecting subcortical structures. Untimely exposure to challenging environmental events or drugs of abuse, in combination with the effects of expression of specific genetic variants may generate dysfunctional circuits, in which changes may have lasting consequences into adulthood psychopathology. So far the best evidence for the functional and neuroanatomical changes in the human adolescent brain that may underlie adolescent psychopathology has been obtained using different applications of structural and functional MRI.

Experiments in animals are providing and will continue to provide details about the basic cellular and molecular mechanisms responsible for the appearance of psychiatric disorders. However, application of knowledge obtained in animals to understanding actual biochemical changes and functional consequences in brain

circuits of human adolescents will require a refinement of imaging, molecular and cellular biology tools. Although logistically challenging, postmortem studies of the adolescent brain in psychiatric disorders would be key to identify specific molecular and cellular alterations in the neurobiology of psychiatric disorders in adolescence. These postmortem studies should define neuronal and glial cell types implicated and the molecular pathways in specific brain gray and white matter regions in adolescent pathology, so that the right experimental questions are put to test in animal models and the right conclusions are drawn about the neuropathological mechanisms underlying neuroimaging findings.

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2 Ecstasy and the serotonin syndrome

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There is presently scarce clinical and basic lab data concerning the risk of acute serotonin toxicity from selective serotonin reuptake inhibitors (SSRIs) and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) co-administration. The health care community would strongly benefit from attending to the high risk of serotonin syndrome from this specific drug combination. Objective: To review the risk of serotonin syndrome in adolescents and young adults prescribed SSRIs who concurrently use ecstasy. Data Sources: An electronic search of the major behavioral science bibliographic databases (Pubmed, PsycINFO, Medline) was conducted to retrieve peer-reviewed articles detailing the clinical characteristics, biological mechanisms and social implications of SSRIs, MDMA, and their potential synergism in causing serotonin syndrome in the pediatric and young adult population.

Search terms included “serotonin syndrome,” “ecstasy,” “MDMA,” “pediatric” and “SSRI.” Additional references were incorporated from the bibliographies of these retrieved articles.

Results: MDMA in combination with the widely-prescribed SSRI antidepressant class can lead to rapid, synergistic rise of serotonin (5-HT) concentration in the central nervous system. This can result in acute medical emergency known as serotonin syndrome. This chapter addresses this complication through an exploration of the theoretical mechanisms and clinical manifestations of this life-threatening pharmacological interaction. Conclusion: Further research, as well as greater health care provider and regulatory body attention to this overlooked and increasingly relevant danger will prevent a growing threat to the public health, owing to the increasing incidences of recreational ecstasy use and SSRI pharmacotherapy among multiple psychiatric disorders in the adolescent population.

2.1 Introduction

MDMA, or ecstasy, is an increasingly prevalent drug of abuse in the adolescent and young adult population (1). Most ecstasy-related deaths occur to teenagers and young adults in the in middle and upper middle class socioeconomic groups (2, 3). The problem appears to be global. More than 4% of the drug-related fatalities documented in the UK, for example, originated from MDMA ingestion (4), and ecstasy abuse resulted in 82 deaths in Australia from 2004 to 2009 (5). The 2003 National Survey on Drug Use and Health (NSDUH) reported over 2,000 young people who presented to the emergency departments across the country reporting MDMA as a major factor in their visit (6). Notably, the incidence of prescription drug use among these populations was unknown; it is likely that a greater incidence of fatality occurred among

individuals receiving medications for a psychiatric morbidity, such as the SSRI class, that potentiates the adverse effects of serotonin elevation.

SSRI therapy is both widespread and rising in adolescents and young adults (7–10). In children, depression disorder is seen in up to 6% and lifetime prevalence rate of depression in adolescence ranging between 15% and 20%, with SSRIs as the main pharmacological approach (8). Given the high comorbidity of psychiatric illness and illicit substance abuse disorders in children and adolescent (11), rising popularity of MDMA, and the rapid increase of SSRI use in patients with psychiatric illness, it is easy to foresee the dangerously high risk of developing acute serotonergic emergency in this specific population (12–14), especially considering the unique and vulnerable biology of the developing human central nervous system (15–18).

2.2 SSRI efficacy and toxicity in adolescents and young adults

Since the introduction of fluoxetine in 1988, the SSRI antidepressant class has become the most widely prescribed antidepressants in the USA across all demographic groups. In 2002, nearly half of all antidepressant prescriptions were SSRIs (19) and today with the help “direct to consumer advertising” this number has enlarged to nearly 100% (20). This pattern is mirrored in the care of child and adolescent psychiatry patient population, with 11% of Americans age 12 and over tried on antidepressants at one time (21), and approximately 2% of children and adolescents in the United States treated with SSRIs (22). The rapid increase of SSRI use in children and adolescents has occurred in spite a scarcity of safety and efficacy data as well as a lack of clear guidelines for use in this population (23). For example, in a large survey of active general pediatricians and family physicians, 72% of physicians reported having prescribed an SSRI for a child or adolescent, despite reported insufficient training in treatment of childhood depression and related psychiatric disorders (24).

SSRI is the first class of antidepressants with rationally engineered mechanisms, efficacy curves and toxicity profiles consistent with intrasynaptic serotonin elevation via a relatively specific inhibition of neuronal reuptake pump for serotonin (5-hydroxytryptamine; 5-HT) (25, 26). It is theorized that SSRIs exert their effect on mood and behavior through elevation of intrasynaptic serotonin level at the nearly 250,000 serotonergic synapses that make up the Raphe nucleus, and innervate prefrontal cortex, hippocampus, and basal ganglia. The broad neuronal network of serotonergic neurons is hypothesized to account for the widespread clinical action of SSRIs including depression, anxiety, and obsessive-compulsive disorder. Inhibition of presynaptic reuptake inhibitors as well as down regulation of 5-HT₁ autoreceptors increase the serotonergic transmission and thereby affect clinical state (27, 28). Additionally, SSRIs are potent inhibitors of the CYP family of liver enzymes (29), creating a potential for a powerful interaction between SSRIs and any pro-serotonergic substance metabolized by the same system, including

other SSRIs (30). Ecstasy is an example of such substance, and as Catterson et al (31) clearly demonstrated, fluoxetine, citalopram and paroxetine have the potential to inhibit CYP2D6 and inhibit metabolism of MDMA.

The most common adverse effects of SSRI toxicity noted in children and adolescents are headache, sedation, nervousness, anxiety, agitation, and insomnia (29), consistent with excessive extracellular serotonin build up. Analyses from various health care centers reported that out of 26,733 cases of SSRI overdose, 14–16% showed some symptoms of serotonin syndrome (32). With concurrent administration of another pro-serotonergic agent, however, the risk of developing serotonin syndrome will undoubtedly increase (33).

2.3 MDMA use in adolescents treated with SSRIs

Synthesized in 1910 and patented in 1912, MDMA was initially used as an adjunct to psychotherapy in the 1950s, but rapidly gained popularity as a recreational “club” drug by the 1980s (34, 35). MDMA is an amphetamine derivative that operates via two different molecular mechanisms to increase central nervous system serotonin concentration. At a typical dose of 1.7 mg/kg, for example, MDMA promotes serotonin neuronal efflux by directly influencing the reuptake transporter and by altering the chemical gradient that moves serotonin away from the intercellular space. The reuptake transporter that MDMA affects to increase serotonin level is the same transporter through which SSRIs exert their pharmacological effects (36). Similar to SSRIs, MDMA is metabolized by and can inhibit CYP2D6. MDMA also follows a non-linear pharmacokinetic metabolism, causing the potential for a disproportionately large rise of MDMA plasma level from a small increase of an oral dose (37).

MDMA administration can cause a number of different acute medical complications, for example, arrhythmias, hypertension, metabolic abnormalities, cerebral hemorrhages, convulsions, and coma (38). Many of these symptoms overlap with those of serotonin syndrome, suggesting that it may be an undercounted and under-appreciated manifestation of ecstasy toxicity (39). Many ecstasy-abusing nightclub patrons display mild signs of the serotonin syndrome (40), and a smaller number develop very severe form of serotonergic over activity with grave medical complications (41).

Beyond acute toxicity, ecstasy has been extensively shown to leave long lasting impairment in crucial higher brain functions, such as cognition and emotional regulation, directly correlated to the degree of use (42). A retrospective study of 66 university age subjects who have been using ecstasy on regular basis were found to manifest impairment with both immediate and delayed recall memory (43). Impulsivity and fixed delusional thought content have also been demonstrated in subjects who have underwent repeated MDMA exposed subjects (44, 45).

2.4 Serotonin syndrome

The signs and symptoms of serotonin syndrome were initially described soon after the introduction of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) for treatment of depressive disorders, but were noted as a significant public health problem secondary to ergot use in Europe as early as the 11th century (46). The effects observed in animal models included enhanced motor activity and excessive excitability, as well as signs of autonomic instability, and finally seizures (47).

Multiple experiments demonstrated a direct correlation between elevation of brain serotonin and increased death rates, after inhibition of MAO-A and MAO-B enzymes together, rather than independently, suggesting a serotonin concentration dependent mechanism of toxicity (48). Given the observations that the concentration of synaptic 5-HT is the main determinant of the severity of serotonin syndrome and the risk of morbidity and mortality, it is essential to gain a better understanding of the capacity of SSRIs and MDMA combination to produce serotonin syndrome as predicted by drug mechanisms, including difference in potency and pharmacokinetics.

Serotonin syndrome can occur by several mechanisms, but excess activation of postsynaptic serotonin receptors appears necessary to produce serotonin syndrome (32). The diagnosis is always made on clinical grounds alone, and there is a broad range in severity and spectrum of symptoms observed. The syndrome is neither rare nor idiosyncratic but is a continuum of signs and symptoms from mild to severe, with mild cases potentially missed or misdiagnosed. An important consideration of serotonin syndrome in the context of “club drug” ecstasy use, especially in the high temperature, and with excess muscle activity, mild cases can quickly convert into serious medical serotonergic emergencies (40, 48, 49). An animal model study has shown a strong correlation between drugs’ ability to raise serotonin levels, measured via microdialysis studies in rats, and the clinical degree of serotonin toxicity, further strengthening the concept of serotonin syndrome as a heterogeneous clinical entity determined by extracellular serotonin concentration (33).

Viewing serotonin syndrome on a spectrum of clinical severity suggests that many patients who are exposed to two or more synergistic serotonin elevating compounds such as SSRIs and MDMA might experience some degree of serotonin syndrome, and will most likely be misdiagnosed to overall clinicians’ lack of familiarity with the milder clinical picture of the syndrome (50). Health care providers must inform their adolescent patients when initiating them on SSRIs, warning that if combined with ecstasy, vigilance of even most mild symptoms should be exercised.

2.5 Ecstasy in combination with SSRI increasing the risk of serotonin syndrome

In theory, any drug, or combination of drugs, which has the net effect of increasing serotonin neurotransmission can produce serotonin syndrome (51). The serotonin syndrome has been reported after co-administration of SSRI and lithium, trazodone, dextromethorphan, for example (52–54). Even an antimicrobial agent Linezolid (55) has been implicated in producing serotonin syndrome in combination with other pro serotenergic drugs, a warning outlined by the FDA in 2001 (56). Opioids such as meperidine, fentanyl, and pentazocine can also precipitate the symptoms of serotonin excess in patients being treated with SSRIs (57–59).

Despite a clear need, basic and clinical science has done little to investigate a physiological interaction between SSRIs and MDMA. This omission is concerning given the powerful potential of both drugs to tremendously raise synaptic cleft serotonin. Microdialysis and measured lab data has shown that SSRIs are capable of very rapid, and large increases of serotonin (5-HT) concentration in animal brains (60–62), and that MDMA administration releases serotonin at various brain sites at a rate possibly above that produced by the SSRIs (63, 64).

The combined pharmacokinetic drug-drug interaction additionally ensues when SSRIs that are also potent CYP450 2D6 inhibitors reduce MDMA metabolism (65, 66). MDMA can conversely exert metabolic effects upon SSRIs metabolism. Paroxetine and fluoxetine administration, for example, has been shown to increase MDMA levels as much as 30% (67). Furthermore, a significant proportion of the world population may be more susceptible to serotonin syndrome when exposed to both MDMA and SSRIs. For example, 8% of the Caucasian population poorly metabolize CYP450 2D6-dependent drugs such as paroxetine and fluoxetine (68, 69). MDMA can also cause hepatic necrosis with reductions in liver function and subsequent drastic decreases in SSRI and MDMA clearance, increasing further the chance of developing serotonin syndrome (70). Moreover, increased body heat from muscle use during prolonged dancing and cooling dysregulation brought about by dehydration can significantly increase body temperature, and through amplified thermodynamic processes cause excessive serotonin release rate (71, 72).

The cultural patterns of SSRI and MDMA use provide grounds for further concern. For example, preemptive use of SSRI either as a function of misguided belief in its neuroprotective effects against MDMA, is popular and a potentially dangerous practice (40, 73–75). Other populations may consume higher doses of MDMA to overcome SSRI's ability to attenuate some of the euphoric – but not toxic – effects of the drug (67). This dangerous effect is further magnified by the non-linear pharmacokinetics of MDMA metabolism that produces disproportionately higher plasma and intercellular concentrations of the drug with increased dosages (76). A survey of 216 young

adults from the Sydney, Australia who had used Ecstasy at least once in the previous 6 months reported 19 cases of purposeful concomitant use of antidepressant medication with MDMA. A considerable number of these subjects took the SSRI either to enhance Ecstasy high or to prevent neurotoxic effects. This sample was analyzed for neuropsychiatric symptoms and a large proportion was shown to display symptoms consistent with serotonin syndrome of various severity (77).

Ecstasy users worldwide are frequently polydrug users, often combining MDMA with other serotonin releasing stimulants, increasing the risk of serotonin syndrome development even further (78–81). A neurotransmitter analysis in animal models, for example, demonstrated that MDMA and methamphetamine administration elevates 5HT level greater than with MDMA alone (82). Moreover, chemical analysis of Ecstasy pills often show myriad of psychoactive chemical additives. For example, a sample of Ecstasy sold on the black market today contain amphetamine derivatives such as MDA, an even more powerful serotonin releaser than MDMA itself (83). This and other amphetamine molecules contained by the Ecstasy pills can release large quantities of serotonin and in combination with SSRIs cause serotonin syndrome (84, 85). A number of clinical reports analyzing MDMA related fatalities showed that most of pills contained amphetamines in addition to or instead of MDMA, and one of the case reports describes death from combination of fluoxetine and MDMA (86).

2.6 Conclusions

The message to the regulatory bodies, physicians and patients should be clear: Ecstasy, in combination with the widely-prescribed SSRIs antidepressant class, can create dangerously high levels of brain and plasma serotonin (5-HT) leading to the acute and sometimes lethal medical emergency known as serotonin syndrome. Given significant amount of psychiatric comorbidity among individuals with substance use disorders, it should not be overlooked that teenagers treated with SSRIs may suffer from MDMA abuse as well. The behavior of people who use Ecstasy often leads to concomitant SSRI use either to augment its affect or to neuroprotect against MDMA toxicity. It is a responsibility of all health care providers, but especially those managing the pediatric population, to communicate to their patients this overlooked and increasingly relevant health danger. Providers who opt to prescribe SSRIs should ask their patients about drug use and attempt to gain collateral information (for example, from parents or friends) to make sure that they do not prescribe SSRIs for an Ecstasy user. Increased awareness and activism among the health care community may produce labeled warnings at the government level, a step which would likely protect this vulnerable patient population from the risk of serotonin syndrome.

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3 Testosterone levels and suicidal behavior

Leo Sher

Several lines of evidence suggest that there is an association between testosterone and suicidal behavior. A link between testosterone and the neurobiology of suicidal behavior may be related to: a) a direct effect of testosterone on suicidality via certain brain mechanisms; and/or b) a testosterone influence on aggression and, consequently, suicidality; and/or c) a testosterone effect on mood and, consequently, suicidality; and/or d) a testosterone effect on cognition and, consequently, suicidality. At least one study has demonstrated a relation between high levels of testosterone and suicide in young people. A significant number of studies suggest that high testosterone levels are associated with aggression in adolescents and adults. Multiple lines of evidence indicate that aggression is associated with suicidal behavior. The effect of high testosterone levels on suicidality in adolescents and young adults may be mediated by testosterone-related elevated aggression. It is also possible that in young people, high testosterone levels are directly linked to suicidality via certain brain mechanisms. In older men, decreased testosterone levels are associated with depressive symptoms and reduced cognitive function while higher blood levels of testosterone are associated with better mood and cognitive functioning. Depression and reduced cognition are associated with suicidal behavior and may mediate the effect of decreased testosterone levels on suicidality. Therefore, it is reasonable to propose that suicidal behavior in adolescents and young adults is associated with high testosterone levels while suicidality in older men is associated with decreased testosterone secretion.

3.1 Introduction

Testosterone, a hormone from the androgen group, was isolated, synthesized and described in the 1930s by European researchers (1). The first research papers on the protein nature and on the isolation of androgen receptors from androgen target tissues were published at the end of the 1960s by several groups of investigators. Confirmation for a specific androgen-binding protein isolated from prostate tissue cytosol, was published by the research groups of Ian Mainwaring from the ICRF in London, Shutsung Liao at the University of Chicago and Étienne-Émile Baulieu at the INSERM Institute in Kremlin-Bicêtre in Paris (2–4).

Testosterone is produced from cholesterol in the Leydig cells in the testis. Testosterone synthesis in the fetal human testis begins during the sixth week of gestation. Leydig cell differentiation and the initial early testosterone production in the fetal testis are independent of luteinizing hormone (LH) (5–7). During testis development production of testosterone occurs under the influence of LH which is produced by

the pituitary gland. Synthesis and release of LH is regulated by the hypothalamus through gonadotropin-releasing hormone (GnRH) and inhibited by testosterone via a negative feedback loop (8). Testosterone is metabolized in some tissues to a more active metabolite, 5 α -dihydrotestosterone.

Testosterone is present in the blood as free (unbound) testosterone, albumin bound and sex hormone-binding globulin (SHBG)-bound testosterone (5–8). Testosterone is a C19 steroid with an unsaturated bond between C-4 and C-5, a ketone group in C-3 and a hydroxyl group in the β position at C-17. It is mostly produced in the testes of males and the ovaries of females, although small amounts of testosterone are produced by the adrenal glands. Testosterone is found in mammals and other vertebrates. Blood testosterone levels are much greater in males than in females: an adult male body produces approximately ten-times more testosterone than an adult female body. Females are more sensitive to testosterone than males. Testosterone regulates male sexual development and affects muscle strength, levels of erythrocytes, bone density, sense of well-being and sexual and reproductive function in both males and females.

SHBG concentrations may be decreased or increased in many frequently observed medical conditions. In clinical practice, changes in SHBG are critically important to consider in the diagnosis of male hypogonadism. Because plasma total testosterone concentrations are affected by alterations in SHBG levels, precise measurements of free or bioavailable testosterone are necessary to evaluate the sufficiency of Leydig cell function, to clarify whether a patient is hypogonadal, and to monitor the testosterone replacement treatment in patients with changes in circulating SHBG concentrations.

3.2 Testosterone and suicide

Multiple studies suggest that testosterone plays a role in the regulation of mood and behavior. The research studies of the relationship between testosterone and suicidal behavior produced variable results (9–14). Some (10–13) but not all (14, 15) investigations of the relationship between testosterone and suicidality found associations between testosterone and suicidal behavior.

Tripodanakis et al compared plasma testosterone concentrations in men after a suicide attempt with testosterone levels in healthy men of the same age (10). The authors found that the suicide attempters had lower testosterone levels compared with controls, and that the attempters who used violent methods had lower plasma testosterone concentrations compared with the non-violent attempters. Markianos et al examined plasma testosterone levels in a group of male psychiatric patients who had attempted to commit suicide by jumping, in a group of male subjects who were hospitalized after unintentionally falling from a high height and in healthy controls (11). Both accident and suicide attempt patients had lower testosterone levels

compared with the control group, and there was a trend towards lower testosterone levels in suicide attempters compared with the accident group. We have recently examined whether there is a relation between plasma testosterone levels and clinical parameters in bipolar suicide attempters and found that testosterone levels positively correlated with the number of manic episodes and the number of suicide attempts (12). Some other observations have shown that testosterone/anabolic androgenic steroids may play a role in the pathophysiology of suicidality (13).

A recent study found no difference between male suicide attempters and male controls with regard to plasma testosterone levels (14). A study of associations between neuroactive steroids and suicidality in military veterans with posttraumatic stress disorder also found no association between serum testosterone levels and a history of a suicide attempt (15).

Disappointment over rejections at attempts for sexual interactions has been cited several decades ago as an important trigger for suicide (16). Impending divorce, marital difficulties, threat of losing a love partner and rejection by a loved one were also regarded as motives for suicide for many years (17). It has been observed that rejection of sexual intercourse was often associated with male suicides and suicidal ideation (18). A link between testosterone and the neurobiology of suicidal behavior may be related to (9):

- (a) A direct effect of testosterone on suicidality via certain brain mechanisms; and/or
- (b) A testosterone effect on aggression and, consequently, suicidality; and/or
- (c) A testosterone effect on mood and, consequently, suicidality; and/or
- (d) A testosterone effect on cognition and, consequently, suicidality.

3.2.1 Testosterone and suicidal behavior in adolescents and young adults

Suicide and testosterone/anabolic androgenic steroids

At least one study has demonstrated a relation between high levels of testosterone and suicide in young people (19). Twenty-nine subjects (17 suicides, 12 sudden deaths) in the ages 23–45 years were included in the study. Analysis indicated no significant difference in ages between the two groups of subjects (suicide $M = 33.35$ year, sudden death $M = 35.67$ year). There was a significant difference in the mean testosterone level ($p < 0.007$) between victims of suicide ($M = 376.41 \div 183.64$ ng/ml) and victims of sudden death ($M = 241.83 \div 117.3$ ng/ml).

Eight cases of suicide, in 21- to 33-year-old males, with a history of current or recent use of anabolic androgenic steroids (AAS) have been described in a case series report (20). Five suicides were committed during current use of AAS, and two following 2 and 6 months after AAS withdrawal. The authors suggested that long-term use of AAS may contribute to completed suicide in predisposed persons.

A possible role of aggression

A significant number of studies suggest that high testosterone levels are associated with aggression (9). It has been shown that violent persons have higher plasma, saliva and CSF testosterone levels compared to non-violent controls (21–23). For example, in a study of impulsive offenders with alcoholism and antisocial personality disorder, higher CSF testosterone levels were observed compared to healthy controls (24). The authors proposed that high CSF testosterone levels may be associated with aggressiveness or interpersonal violence. In the same paper, the authors reviewed the scientific literature on the link of testosterone to aggression in humans, and proposed that both a repetitive pattern of aggressive behavior starting early in life, and a repetitive pattern of aggressive behavior under the effect of alcohol are associated with increased levels of testosterone. Researchers have observed that individuals receiving testosterone are more likely to have an aggressive reaction to perceived threats than subjects receiving placebo (25–27).

Fluctuations of testosterone concentration may be associated with aggression and mood changes in adolescents (28–30). Salivary testosterone concentrations were evaluated in 40 children, aged 7–14 years (37 boys and three girls), with a history of aggressive behaviors and an association between higher testosterone levels and aggressive behaviors was observed (29). In another study of adolescent males, higher testosterone levels were associated with provoked verbal and physical aggression, a finding suggesting that reactive impulsive aggression is correlated with higher testosterone levels (30). Fifty-eight healthy 15–17-year-old boys, public school students participated in this study. A high level of testosterone led to an amplified readiness to respond energetically and forcefully to provocations and threats. Testosterone also had an indirect and less strong effect on another aggression dimension: high plasma concentrations of testosterone made the boys less patient and more irritable, which in turn intensified their predisposition to engage in aggressive-destructive behavior. Therefore, aggression may mediate the effect of high testosterone levels on suicidal behavior in adolescents and young adults. Not all studies have observed differences in testosterone levels between aggressive and non-aggressive boys (31). A study of 4–10 year olds found no evidence of a relationship between testosterone levels and aggressive behaviors. This indicated that such a relationship may be non-existent in prepubertal children.

Animal models have contributed important data regarding the effects of anabolic androgenic steroid (AAS) use on aggression (32, 33). For example, studies in rodents confirmed that exposure to the AASs testosterone and nandrolone increases aggression. A side effect of AAS use reported in humans is “roid rage,” a state of unselective and unprovoked aggression. It has also been observed that pubertal rats receiving AASs respond appropriately to social cues and they are more aggressive toward intact males than are castrates. Testosterone-treated male rats are most aggressive in their home cage. Probably, adolescent AAS exposure may increase aggressive behaviors.

Some authors have postulated that there are substantial similarities between aggression against the self and aggression against others, based on the clinical and epidemiological observations that some suicide attempters may share personality traits with violent criminals (34). We have also observed an association between aggression and suicidal behavior in our studies (35, 36). For example, we have observed that a history of suicide attempt in bipolar disorder is associated with lifetime aggressive traits (35). We have also shown that the higher prevalence of suicide attempters among depressed patients with a history of alcoholism compared to depressed patients without a history of alcoholism was related to higher aggression scores in the group with alcoholism (36).

In summary, high testosterone levels may be associated with suicidal behavior in adolescents and young adults. This effect of testosterone on suicidality in adolescents and young adults may be mediated by testosterone-related elevated aggression. It is also possible that in young people, high testosterone levels are directly linked to suicidality via certain brain mechanisms.

3.2.2 Testosterone and suicidal behavior in older men

Testosterone deficiency or hypotestosteronemia is a commonly known hormonal change associated with male aging (37–39). The prevalence of testosterone deficiency may be as high as 30% in men aged 40–79 years (40, 41). In up to 12% of affected men, hypotestosteronemia can be associated with clinical symptoms (40, 41). Age-related plasma testosterone decrease is a result of different biological alterations such as primary structural gonadal damage, age-related degenerative changes of the pituitary gland, insufficiencies of the neurohypothalamic system, and primary peripheral metabolic abnormalities such as the age-associated increase in the concentration of serum SHBG, with a consequent decrease in free testosterone (39). In the aging man, there is about a 1–2% decrease of total testosterone levels per year with a more rapid drop in free testosterone levels because of a concomitant increase in SHBG with aging. Because of this gradual decrease in testosterone levels the androgen deficiency of the elderly man is defined as partial androgen deficiency of the aging male (PADAM) or late onset hypogonadism (LOH).

Symptoms of testosterone deficiency in men include sexual symptoms (such as reduced erectile function and diminished libido), decreased muscle and increased fat mass, and reduced bone density among others. It is unclear whether aging is to be considered as the only variable linked to age-related testosterone decrease. Various aspects such as genetic factors, chronic diseases, medications, obesity, and the lifestyle may affect the testosterone metabolism (37, 42–44).

Decreased testosterone levels are associated with depressive symptoms, poor cognitive function and Alzheimer's disease (9, 45–48). Increased incidence of hypogonadism is observed in men with major depression (9, 47). Depressed men frequently

have low plasma or serum testosterone (9, 48). Testosterone has mood-enhancing properties and antidepressant effects in men (9, 49–51). Testosterone replacement effectively improves mood. Testosterone users sometimes develop manic or hypomanic symptoms during testosterone use and depressive symptoms during testosterone withdrawal (52–55). In rodents, testosterone has antidepressant effects in aged male mice and protective effects against the development of depression-like behaviors in rats (56, 57). A recent study found a testosterone-dependent regulation of hippocampal ERK2 expression which suggests that ERK2 signaling within the dentate gyrus area of the hippocampus is a vital mediator of the antidepressant properties of testosterone (58).

Experimental studies suggest that testosterone has neuroprotective effects (59). However, intervention clinical research on elderly men showed that testosterone replacement had a beneficial influence on mood only if men had clearly subnormal testosterone levels (60). It is important to note that sexual dysfunction can have a major effect on the quality of life and emotional well-being (61, 62). The results of placebo-controlled randomized studies of the effects of testosterone on the quality of life and depressed mood have been inconsistent and often the quality of life as assessed by different questionnaires did not improve significantly (63).

Higher blood levels of testosterone are associated with better cognitive functioning, especially in older men (45, 46). For example, greater serum levels of testosterone late in life predict a lower risk of future Alzheimer's disease development in older men (45). Higher blood testosterone levels are associated with better visuospatial abilities, semantic memory and episodic memory in men, with larger positive effect with increasing age (46).

Both depression and cognitive impairment are associated with suicidal behavior (64–67). At least 60% of individuals who commit suicide suffer from depression. Hence, depression and cognitive impairment may mediate the effect of testosterone deficiency on suicidality in older men. This suggests that the treatment of hypogonadism in older men may improve mood and cognition, and consequently, reduce suicidal behavior.

3.3 Conclusions

In summary, it is reasonable to propose that suicidal behavior in young men is associated with high testosterone levels while suicidality in older men is associated with decreased testosterone secretion. This indicates that the effects of testosterone on suicidality in men should be studied separately in young and old individuals. It is likely that plasma and salivary testosterone assays can help in identifying pediatric and adult patients that would respond best to certain treatments. Further studies of the role of testosterone in the pathophysiology of psychiatric disorders and suicidal behavior are merited.

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4 Buprenorphine in the treatment of non-suicidal self-injury

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A global public health problem, non-suicidal self-injury (NSSI) is highly prevalent in both males and females, and tends to first occur in adolescence. NSSI is correlated with a history of childhood trauma, and with a variety of developmental and psychiatric disorders. NSSI is associated with increased risk of morbidity and premature death from suicide, accidents, and natural causes. Current treatment approaches are inadequate for a substantial number of people. Converging evidence for opioid system dysregulation in individuals with NSSI make this a promising area of investigation for more effective treatments. The pharmacological profile of buprenorphine, a potent μ -opioid partial agonist and κ -opioid antagonist, suggests that it may be beneficial. In this chapter we describe the successful treatment of severe NSSI with buprenorphine in six individuals, followed by discussion and further recommendations.

4.1 Introduction

Non-suicidal self-injury (NSSI) is an important public health problem with first onset commonly occurring during adolescence (1, 2). Individuals who engage in NSSI have double the expected all-cause mortality rate and are at increased risk of death from suicide, accidents, and natural causes compared to the general population (1–5). NSSI behaviors co-occur with a variety of psychiatric disorders, are associated with high health care utilization, and greater functional impairment (6–10). Concerns regarding clinical representation and management of NSSI have prompted the proposed inclusion of NSSI Disorder into the Diagnostic and Statistical Manual of Mental Disorders (11). NSSI is generally defined as the intentional, direct destruction of body tissue without suicidal intent, and for purposes that are not socially sanctioned (12). Occurring equally often in men and women, the estimated prevalence is 4% in the general population and 21% in clinical samples (9, 10, 13, 14). A recent literature review of NSSI among adolescents indicates a lifetime prevalence range from 13–23% (1). About 70% of adolescents engaging in NSSI reported a lifetime history of suicide attempt and 55% reported multiple attempts (15).

There is a clear medical need for new drugs that would expand the options for treating NSSI, especially for the substantial number of patients with NSSI who do not respond to existing treatments. Endogenous opioids have been implicated in the expression of NSSI in psychiatric and developmental disorders, including borderline personality disorder, major depression, mental retardation, and autism (16–18). There are observations suggesting that opioid antagonists can be used for the treatment of NSSI in patients with borderline personality disorder, depression, anxiety,

developmental, and other psychiatric disorders (19–23). Multiple reports demonstrate that naloxone or naltrexone is useful in diminishing NSSI (19–23). For example, in an open study, six of seven female patients with NSSI treated with naltrexone had complete remission of NSSI, and the seventh had significant reduction of NSSI (23). The use of opioid antagonists for the treatment of NSSI may lead to tapering or discontinuation of antipsychotics and mood stabilizers that have significant metabolic and other side effects.

Examining the efficacy of buprenorphine for the treatment of NSSI is probably a promising avenue of research. Buprenorphine is available and used safely for the treatment of physical dependence to opioids (24) but has received virtually no attention for the use in psychiatric disorders in non-dependent populations. As a μ -opioid receptor partial agonist and κ -opioid antagonist, buprenorphine has been studied extensively in animal models of drug reward, physical dependence, and analgesia (25–27). The pharmacological profile of buprenorphine as a potent μ -opioid partial agonist and κ -opioid antagonist suggests that buprenorphine may produce beneficial effects on patients with NSSI. Taken together, the existing data suggest that there is a foundation for considering the use of buprenorphine for new indications in psychiatric disorders including NSSI. In this paper, we report on six cases of successful treatment of NSSI with buprenorphine.

4.2 Clinical approach

This is a descriptive case series of six long-term psychiatric inpatients with severe, treatment refractory NSSI whose usual treatment was augmented with buprenorphine. The Institutional Review Boards of the Capital District Psychiatric Center and the New York State Office of Mental Health approved the case series protocol. The treating psychiatrist independently initiated treatment and adjusted the dose of buprenorphine according to response, and confirmed the participant's capacity to consent to the case report. Data was collected from patient interview and a retrospective review of the medical record. Three outcomes were examined: all reported incidents (e.g., assault, self injury, falls, elopement, etc.), NSSI episodes, and seclusion and restraint (S/R) episodes. For the purpose of statistical analysis, a comparison was made between the average monthly number of overall incidents, NSSI episodes, and S/R episodes without buprenorphine treatment, and the average number with buprenorphine treatment. A t-test comparison was used to determine the significance of the differences between these two data sets. t-Values were calculated for the overall combined data from all patients, and for each individual patient in the study. The t-value was calculated by dividing the overall increase or decrease from the baseline over the standard deviation of post treatment data divided by the square root of the number of post treatment data points.

4.3 Case descriptions

All six individuals are characterized by having long histories of severe repetitive NSSI behaviors refractory to more conventional approaches resulting in severe functional impairment. Persistent NSSI has been a major barrier to attainment of satisfactory quality of life, wellness, school and occupational achievements, and has resulted in lengthy, numerous psychiatric hospitalizations since childhood. Invariably there has been a history of severe and recurrent interpersonal trauma and violence in childhood, including physical, sexual and emotional abuse and neglect. The complexity of their psychological and social issues and the inadequate integration of social medicine approaches leads to them amassing multiple, disparate psychiatric diagnoses, and being exposed to numerous medications of limited benefit. Every participant has had suboptimal response to various combinations of medications (e.g., antipsychotic medications including clozapine, antidepressants, mood stabilizers including lithium, valproate, and carbamazepine, benzodiazepines, alpha-adrenergic and beta-blockers, and the opiate antagonist naltrexone), and individual and group treatment (e.g., cognitive behavioral therapy, dialectic behavioral therapy, behavior contracts, social skills training, expressive therapy, wellness, recreation, and psychoeducation). Basic patient characteristics are summarized in Table 4.1. Buprenorphine treatment results for each patient and in aggregate regarding the three outcome measures are presented in Table 4.2.

Case 1

This 34-year-old single, unemployed woman has a history of childhood neglect, physical abuse, sexual abuse and chronic institutionalization. Serious disruptive and self-destructive behavior began at the age of 4, leading to her first psychiatric

Table 4.1: Patient characteristics

Case	Age at trial (years)	Sex	Age, first admission (years)	Substance abuse history	Number psychiatric admissions*	Time period	% days inpatient
1	34	F	6	O, A, Ca, H	17	1992–2012	100
2	29	F	15	O, A, Ca, B	22	2008–2012	**
3	29	F	12	O, A, Ca, Co, D	23	1985–2012	40
4	26	M	10	A, Ca	14	2003–2012	70
5	24	M	16	A	13	1994–2012	50
6	40	M	17	A, Ca, Co	4	1988–2012	62

O: opioid, A: alcohol, Ca: cannabis, Co: cocaine, D: diphenhydramine, H: hallucinogen, B: benzodiazepine abuse or dependence.

* Information available from medical record lacked details from some earlier admissions.

** Most recent hospital stay = 429 days, details of other inpatient data unavailable.

Table 4.2: Total number of reported incidents, NSSI episodes, and S/R episodes with and without buprenorphine treatment for individual cases and all cases combined

Case	Total incidents (average per month)		p-value	NSSI episodes (average per month)		p-value	S/R episodes (average per month)		p-value
	-BUP	+BUP		-BUP	+BUP		-BUP	+BUP	
1	6.80	3.11	<0.01	3.13	1.44	<0.01	17.00	4.11	<0.01
2	2.67	1.69	<0.05	1.33	0.77	<0.05	2.33	0.92	<0.05
3	1.78	0.29	<0.01	1.67	0.00	*	0.67	0.00	*
4	2.33	1.45	ns	2.00	1.36	ns	2.77	0.64	<0.01
5	8.00	3.00	**	4.00	2.00	**	4.00	0.00	**
6	1.20	1.57	ns	0.80	0.86	ns	1.20	0.29	<0.01
Combined	3.43	1.71	<0.01	2.04	0.96	<0.01	6.27	1.21	<0.01

-BUP: without buprenorphine treatment, +BUP: with buprenorphine treatment.

NSSI: non-suicidal self-injury, S/R: emergency seclusion or restraint, ns: non-significant.

* unable to calculate p-value due to zero NSSI and S/R episodes during active treatment period.

** unable to calculate p-value due to short duration of active treatment.

hospitalization at age 6. Intermittent inpatient admissions throughout childhood were followed by the current continuous hospitalization that began in early adolescence. Repetitive, impulsive NSSI and aggressive behavior towards others have been prominent features of her presentation throughout. Over the course of mental health treatment, she has received various diagnoses including: attachment disorder of childhood, oppositional defiant disorder, pervasive developmental disorder, major depressive disorder without psychotic features, chronic post traumatic stress disorder (PTSD), impulse control disorder, borderline personality disorder, personality disorder not otherwise specified with narcissistic and borderline traits, and substance abuse (alcohol, cannabis, opioids, and hallucinogens). She has claimed to have deliberately engaged in some NSSI for the purpose of being treated with opioid pain medications. NSSI includes foreign body ingestion, foreign body insertion into body orifices or under the skin, cutting, banging head or limbs, refusing urgent medical care, deliberate disruption of blood glucose control, reopening wounds, and provoking others to assault her. Her NSSI has led to serious harm and several life threatening injuries, including a nearly fatal intake of disinfectant solution, and esophageal perforation from foreign body ingestion. Medical history is significant for obesity (BMI = 40), juvenile onset insulin dependent diabetes mellitus, and gastroesophageal reflux disorder. There is an unconfirmed history of head injury at age of 11 due to exiting a moving vehicle. Laboratory screening and evaluation for chronic inflammation, heavy metal levels, vitamin B12, folate, endocrine disorders and chronic infectious diseases were negative. Computed tomography of the head at age 24 showed mild cortical atrophy. Due to ongoing life disruptions, she never finished high school. Psychological testing scores are as follows: Weschler Intelligence Scale for Children, revised

(WISC-R) full scale 95, verbal 95, performance 96 (age 11), full scale 71, verbal 79, performance 67 (age 13), and Weschler Adult Intelligence Scale, revised (WAIS-R) full scale 75, verbal 76, performance 77 (age 18). A neuropsychiatry consult was obtained when the patient was 28-year-old which concluded that there was no compelling evidence a traumatic brain injury, and attributed the patient's intellectual decline and mild cortical atrophy to a process of neurodevelopmental failure in the context of impaired attachment and chronic institutionalization.

A buprenorphine trial was started with the aim to reduce mood dysregulation, impulsive NSSI, aggression towards others, and S/R episodes. The patient received buprenorphine/naltrexone 2/0.5 mg sublingually for 2 days, then 1/0.25 mg sublingually for 15 days, reduced because of dizziness. After 17 days of treatment, the patient refused the medication despite rapid subjective and objective improvement in the target symptoms. She stopped treatment due to abandonment fears; staff complimented her on rapid and marked improvement and she believed she would lose their close attention and care. After 18 days without medication she admitted she felt better with the treatment and commenced a second trial of buprenorphine/naltrexone 1/0.25 mg daily for 30 days. Buprenorphine alone was continued thereafter with a dose range of 0.5–3 mg daily. Overall, 15 months of treatment without buprenorphine was compared to nine months of buprenorphine treatment data. The patient had a significant reduction in total incidents, NSSI, and S/R episodes while taking buprenorphine. Subjectively the patient reported a marked improvement in her chronically dysphoric mood and stated: "I'm less depressed. I still have impulsive thoughts but I don't feel like I need to act on them, I can focus on other things I like to do."

Case 2

This 29-year-old single, unemployed woman has a history of childhood physical, sexual and emotional abuse beginning at age 6. She was repeatedly sexually and physically abused in subsequent adolescent and adult relationships. She has had over 20 psychiatric hospitalizations beginning in adolescence for depressed mood, NSSI, and suicidal thoughts or attempts. NSSI includes cutting, high-risk sexual activity, and overdosing on medication. She reports that cutting and drug use have helped to relieve emotional distress. Over the course of psychiatric treatment, diagnoses have included: chronic PTSD, depressive disorder not otherwise specified, nicotine dependence, other substance abuse (heroin, cannabis, benzodiazepines, and alcohol), and borderline personality disorder. She completed 1 year of college. Psychological testing with the WAIS-IV indicated a full scale IQ of 80. Medical history is significant for hypothyroidism, obesity (BMI = 48), obstructive sleep apnea, gastroesophageal reflux disease, irritable bowel syndrome, asthma, and chronic pain secondary to degenerative disc disease.

She was started on buprenorphine and titrated up to 2 mg twice daily. Three months of pre-treatment data was compared to 3 months of buprenorphine treatment data. Buprenorphine treatment was associated with significant decreases in

total number of incidents, NSSI, and S/R episodes. Sustained improvement in NSSI and mood facilitated discharge to a community residence and outpatient treatment after 14 months of inpatient care. As an outpatient, she has continued to take buprenorphine/naltrexone daily and has not used drugs or alcohol. At the time of this writing, she has spent 3 months in the community, and has had no readmissions. She has reported mild mood fluctuations, occasional “voices” telling her to harm herself that she can generally ignore, and has remained free of NSSI behaviors. The patient feels strongly that the buprenorphine/naltrexone has helped significantly with her mood and NSSI, and reports that prior to using the medication she was having urges to self-harm on a daily basis.

Case 3

This 29-year-old single, unemployed woman has a history of neglect, severe emotional, sexual, and physical abuse (including kidnapping, physical and sexual torture), during childhood. She has a history of over 15 instances of residential treatment and psychiatric hospitalizations beginning at age 12 for NSSI, suicidal behavior, depression, aggression towards others, and abuse of drugs including alcohol, opiates, cannabis, and diphenhydramine. NSSI behaviors include cutting, biting, banging her head, dropping heavy objects on extremities, overuse of medications, substance abuse, and starving herself. As an adolescent she was diagnosed with anorexia and bulimia, conduct disorder, attention deficit hyperactivity disorder, and PTSD. Additional diagnoses have included major depressive disorder, dissociative disorder, schizoaffective disorder, and borderline personality disorder. Developmental history is significant for premature birth and developmental delays in speech and motor functioning. Medical history is significant for obesity (BMI = 46), GERD, and asthma. She has bilateral 70% sensorineural hearing loss due to physical abuse in childhood. Psychological testing with the Wechsler Abbreviated Scale of Intelligence (WASI) showed a full-scale IQ score of 95. On the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a screening measure of cognitive ability, her performance across the different domains of functioning was within normal limits.

She was initially treated with buprenorphine 2 mg twice daily but complained of fatigue. The fatigue abated with a reduction to 2 mg daily that was maintained until discharge. Nine months of data without buprenorphine treatment were compared to 7 months with treatment. While taking buprenorphine, there was a significant decrease in total incidents. There were no episodes of NSSI or S/R while she received the medication. She was discharged from hospital after 4 months of sustained response. Despite the dramatic decrease in impulsivity and NSSI observed and reported by the patient, her outpatient treatment provider had concerns about substance abuse and the lack of evidence in the literature and discontinued buprenorphine. Although details are limited, once buprenorphine was stopped the patient restarted engaging in NSSI and has had multiple psychiatric admissions. The potential rapid, marked, and sustained benefit observed in these highly symptomatic individuals should be

weighed against legitimate concerns regarding substance abuse. Such risks could be mitigated with careful monitoring.

Case 4

This 26-year-old single, unemployed man with a history of psychiatric treatment since age 8 has had multiple inpatient admissions since age 10 for severe NSSI and aggressive behaviors. His NSSI consists of severe cutting, biting and head banging. During childhood he repeatedly witnessed physical violence between his parents and was sexually abused. The patient has had a variety of diagnoses including attention deficit hyperactivity disorder (ADHD), conduct disorder, PTSD, schizo affective disorder, borderline personality disorder, and borderline intellectual functioning. Medical history is significant for asthma, non-insulin dependent diabetes mellitus, and obesity (BMI = 41). He attended special education classes from 4th through 8th grade, then frequent hospitalizations and severe behavioral disturbances interrupted formal schooling. Intelligence is estimated to be in the low average range. Despite some decrease in impulsivity with clozapine and antidepressant medications, the patient continued to have severe impulsive NSSI, emotional dysregulation, and dissociative symptoms. The impulsivity and NSSI did not respond to several long trials of naltrexone in doses up to 100 mg daily.

The patient received buprenorphine up to a dose of 2 mg three times daily. Thirteen months of data without buprenorphine treatment was compared to eleven months with buprenorphine treatment. Treatment was associated with a non-significant decrease in total incidents, NSSI episodes, and a significant reduction in S/R episodes. The patient reports that the medication “helps my mood and I don’t want to hurt myself as much when I take it.”

Case 5

This is a 24-year-old single, unemployed man with a history of psychiatric treatment since age 15. Since adolescence he has had over 20 hospitalizations for depression, suicide attempts, and difficulty regulating intense emotions and impulses. He has frequently engaged in NSSI, mainly severe cutting, in response to intense anger, agitation, hopelessness, and interpersonal conflicts. He has denied a history of physical or sexual trauma, but reports being verbally bullied in school because of his appearance. Psychiatric diagnoses have included ADHD, bulimia nervosa, depressive disorder not otherwise specified, alcohol abuse, cannabis abuse, nicotine dependence, and borderline personality disorder. Psychological testing with the WAIS-IV revealed a full scale IQ in the average range. Medical history is significant for hypothyroidism and vitamin D deficiency.

The patient took buprenorphine for 14 days and discontinued it due to nausea. Despite the short course of treatment there was a rapid reduction in impulses to self-harm, and a decrease in incidents and restraint episodes that persisted for at least 12 months after buprenorphine discontinuation. This allowed him to benefit more

fully from treatment, attain the skills and stability that facilitated discharge to the community. The patient stated: “When I took the medication the idea of cutting myself made me sick, I don’t want to do it anymore.”

Case 6

This 40-year-old single man has a history of psychiatric hospitalizations since late adolescence and has been almost continuously hospitalized for over a decade for severe depression, emotional dysregulation, NSSI, and suicide attempts. NSSI behaviors include cutting, piercing, burning, as well as engaging in drug use and high-risk sexual activity. There is a history of repetitive intrafamilial childhood sexual abuse. Developmental milestones were reported to be normal, however he attended special education classes starting in fifth grade. Psychological testing places his full scale IQ in the borderline intellectual range. Psychiatric diagnoses have included major depressive disorder, PTSD, paraphilia, polysubstance dependence (alcohol, cannabis, and cocaine), borderline personality disorder, and borderline intellectual functioning. Medical history is significant for hyperlipidemia, vitamin D deficiency, obesity (BMI = 30), and andontia.

He was treated with 2–4 mg of buprenorphine daily. Data from ten months without treatment were compared to seven months during which the patient received buprenorphine. With treatment, the total number of incidents and NSSI slightly increased but the change was not significant. Episodes of S/R decreased significantly. The patient reports “I’m not sure if it helps or not, maybe sometimes.”

4.4 Discussion

Buprenorphine is a partial μ -opioid receptor agonist with high affinity but low intrinsic activity. In addition to its effects on the μ receptor, buprenorphine also displays antagonistic activity at the δ - and κ -opioid receptors. In addition, buprenorphine also possesses affinity for the nociceptin/orphanin FQ (ORL1) receptor (28, 29). Due to its partial agonist properties with limited intrinsic efficacy, buprenorphine can behave as a pure μ agonist, yet it can also antagonize the actions of morphine and other high-efficacy μ agonists (30, 31), i.e., it can have either μ -agonistic or μ -antagonistic effects, depending on the particular conditions under which it is evaluated. Buprenorphine exhibits antinociceptive effects when a low intensity stimulus (e.g., 50°C water) is used but not when a high intensity stimulus (e.g., 55°C water) is used in a tail withdrawal test in rhesus monkeys (32). Buprenorphine can also attenuate the antinociceptive effects of higher efficacy agonists, e.g., alfentanil when it does not itself have antinociception actions (32, 33). Buprenorphine displays an inverted U-shaped dose-response function, e.g., in analgesia (34, 35). The actions of buprenorphine may vary significantly depending on the environment/circumstances/conditions surrounding its administration and the dose administered.

Although buprenorphine penetrates rapidly into the brain, it associates only slowly with the μ receptor, and its dissociation rate is exceptionally long (36, 37). If a μ -opioid receptor antagonist is injected once buprenorphine already has had time to associate with the receptor and produce its effects, these effects cannot or can only partially be antagonized by naloxone or naltrexone (34, 38). Buprenorphine has a remarkably long duration of action. Behavioral effects of single drug administration of buprenorphine have been found to persist even after several (up to 10) days in different procedures and paradigms in rats and monkeys (39–45). Dynorphin is associated with κ receptor activity and appears to be involved in chemical-induced and pressure-induced pain perception (46). Steiner and Gerfen (47) suggest that the specific function of dynorphin and enkephalin is to dampen excessive activation of projection neurons by dopamine and other neurotransmitters, and have proposed that dynorphin may be involved in the mechanisms of behavioral sensitization. The roles of beta-endorphin, met-enkephalin, and dynorphin may differ in NSSI because they play different roles in pain perception and behavior (16). If the endogenous opioid system is central to repetitive NSSI, then treatment with a long-acting opioid antagonist could block the reward of enhanced endogenous opioids caused by such behaviors and subsequently lead to their extinction (16).

Limitations should be noted:

- (a) this is not a controlled trial, there is no placebo group to compare and it is limited to a small sample of only six patients;
- (b) there are multiple confounding variables:
 1. a concomitant use of psychotropic medications;
 2. it is possible that patients treated with buprenorphine received more attention from the treatment team; and
 3. it is possible that there was a selection bias when these six patients were chosen for the buprenorphine trial.

4.5 Conclusions

Mounting evidence suggests that the endogenous system may be involved in NSSI. Thus, opioid receptor modulators may be able to contribute to beneficial alterations in NSSI. These six case reports demonstrate very impressive results of buprenorphine treatment for NSSI. This preliminary data reveals that buprenorphine may conceivably be an alternative therapeutic option to treat NSSI. Buprenorphine is abusable in part due to its opioid agonist effects, especially by individuals who are not physically addicted to opioids. This may lead to opposition towards the study and use of buprenorphine as a treatment for NSSI. However, buprenorphine is not likely a first-line candidate for the treatment of NSSI, but rather reserved for circumstances of NSSI that are refractory to traditional therapy. The balance of evidence appears to be in favor of future studies of the role of buprenorphine in the management of NSSI. More

research including observational and pilot studies, and randomized controlled trials is needed to examine the usefulness of buprenorphine in the treatment of NSSI and to develop effective treatment regimens.

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Section II: **Depression**

5 Antidepressants for major depressive disorder in children and adolescents

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Major depressive disorder (MDD) is a frequent condition among children and, especially, among adolescents, although its clinical presentation usually differs from that of adults. It is associated with other diagnoses and with an increased morbidity and mortality. However, MDD in this population remains under-recognized and under-treated. Antidepressants (ATD) are chosen when psychoeducational, psychosocial and/or psychotherapeutic approaches have failed. They are generally used in severe cases, always in combination with psychological treatments. The objective of this work is to discuss the role of ATD for child and adolescent MDD. We focus on the recommendations of the most cited and updated clinical guidelines and discuss some controversial aspects with regard to efficacy and safety issues raised based on the information obtained from clinical trials. Finally, we offer some practical recommendations for clinicians. All these findings also pose some doubt on the hypothesis of MDD as a homogeneous phenomenon during the human life cycle.

5.1 Introduction

Depressive disorders are frequent conditions among children and adolescents. In the US, the 12-month prevalence for depressive disorders is said to be 3.7%, 2.7% for major depressive disorder (MDD), and 1.0% for dysthymia (1). Five to ten percent of children and adolescents suffer subsyndromal symptoms of depression that, nonetheless, cause significant impairment (2). During childhood, prevalence is similar in men and females; however, after puberty it becomes twice as frequent in women compared to men. The risk of MDD begins to rise since early adolescence. In community samples, the median age of onset of MDD is 13 years and the cumulative incidence by age 18 is 18–20% (3, 4).

Child and adolescent depression is a serious disorder associated with a high-risk of suicidality, recurrence, and chronicity (5–7). MDD is usually related to significant deleterious effects on the child's normal development, familial and/or academic functioning. Besides, it is frequently comorbid with other diagnostic conditions such as substance use disorders, personality disorders and/or behavioral disorders (8), and it increases suicidal risk; in fact, as many as 50% of adolescents with suicidal behaviors meet diagnostic criteria for MDD (9–12).

From the phenomenological point of view, the clinical presentation of depression among adolescents, but especially among children, differs from that of adult patients. Therefore, although depression is not uncommon in both populations, it is not presented with the same signs and symptoms as during adulthood. The clinical

description of MDD in current diagnostic manuals should be modified when approaching children and adolescents; it is frequent to observe behavioral or physical manifestations instead of cognitive or emotional well defined complaints. Moreover, there are significant differences with regard to treatment responses in adolescents compared to adults (psychotherapy proves to be more effective than ATD), and depression in these years is more associated with some specific, emotional stressful conditions compared to adults. These clinical aspects should be always taken into account and pose some doubt on the hypothesis of MDD as a homogeneous phenomenon during the life cycle.

In any case, effective treatment of depression in this population may reduce its negative impact on psychosocial functioning and may lessen the risk of other adverse psychiatric sequelae. Unfortunately, only 25% of children and adolescents suffering MDD are estimated to be properly diagnosed and treated (13, 14). Preventive efforts should focus on early detection of first and recurrent episodes of depression as well as in identifying risk factors for MDD and/or its comorbid conditions.

The aim of this work is to discuss the role of antidepressants (ATD) when treating children and adolescents who suffer MDD. We focus on the recommendations of the most cited and updated clinical guidelines and address some critical aspects with regard to efficacy and security issues raised after the information obtained from clinical trials. Finally, we offer some practical recommendations for clinicians.

5.2 Treating child and adolescent depression: an overview

Antidepressants are one out of a wide range of interventions in children and adolescent with MDD though they are not considered its first line treatment. All clinical guidelines recommend that first line interventions should include brief psychoeducational treatment (education about depressive signs and symptoms, sleep hygiene, anxiety management, and regular exercise) as well as psychosocial approaches (addressing recent family or peer group conflicts, problem solving strategies, and attention to parental psychopathology, particularly depression). Recent studies estimate that these interventions can achieve a significant improvement in a substantial proportion of depressed patients, and not only in mild MDD but also in up to 20% of adolescents with severe MDD (15, 16).

When this basic routine care is not enough, or in children and adolescents with moderate to severe, chronic or recurrent depression, risk of suicidality or significant psychosocial impairment, patients should be referred to a specialist care clinic (3, 17). In those cases, the next therapeutic option should be psychotherapy (brief family therapy, interpersonal therapy or cognitive behavioral therapy). In cases of severe MDD or when previous approaches have failed, antidepressants (ATD) should be considered, along with the combination/augmentation psychotherapy (especially cognitive behavioral therapy) the next therapeutic option.

Antidepressant-only treatment is not recommended with the exception of extremely severely depressed patients whose condition unable them to go into psychotherapy (3). However, as soon as the adolescent is amenable to psychotherapy, combination therapy (i.e., ATD and psychotherapy) should be provided. Therefore, there is a limited role for ATD when treating children and adolescent MDD. In cases where ATD are indicated, they should generally be combined with psychotherapy.

With regard to which ATD drugs should be used, only fluoxetine and escitalopram have been approved by the US Food and Drug Administration (FDA) for acute and maintenance treatment of MDD in this population. These restrictions are due to the limited success of ATD versus placebo in most randomized controlled trials (RCT) conducted in the last decades, particularly in children below the age of 12 years (18–20). However, response rates are usually high, ranging from 30% to 60% (21–23), and similar to those observed with ATD treatment for obsessive-compulsive disorder (OCD) or non-OCD anxiety disorders (24). Nevertheless, the main difference is that the response to placebo is higher for youths with MDD (50%) when compared with placebo response for those with OCD and non-OCD anxiety disorders (32% and 39%, respectively) (25). In a recently meta-analysis, Bridge et al (25) concluded that a higher rate of patients taking placebo who responded to treatment was associated to multi-site trials, milder depression at baseline and younger participants. This fact suggests that pharmacotherapy studies of pediatric depression that include only patients over 12 years of age, with at least moderately-severe depression, may be more informative and efficient than most recent clinical trials.

5.3 Efficacy

Available studies assessing the efficacy of ATD in children and adolescents are scarce, compared to those in adult samples, and of variable quality. Some have design, methodological and/or analytical problems that make cross-comparisons difficult (i.e., different psychometric evaluations, variability of outcomes, etc.). In fact, most primary outcomes usually refer to changes in clinical rather than in functional scales. In addition, secondary outcomes are generally subjective measurements (e.g., changes in the Clinical Global Impression Scale, CGI). Some studies have failed to demonstrate significant efficacy in primary outcomes but have suggested significant differences versus placebo in secondary outcomes (23). Moreover, significant changes in symptom scales do not always correlate with relevant clinical changes and studies are often too short to assess functional changes, long-term efficacy, and relapse rates (20).

Some well-designed placebo-controlled trials, like the Treatment for Adolescent Depression Study (TADS) funded by the National Institute of Mental Health (NIMH), have tried to evaluate the short and longer-term effectiveness as well as the durability of SSRIs. In particular, the TADS evaluated the efficacy of four treatments among adolescents with MDD, at 12 and 36 weeks with a 5-year naturalistic follow-up: clinical

management with fluoxetine, cognitive-behavioral therapy (CBT), combined fluoxetine plus CBT, and clinical management with placebo (26). However, even in such a well-designed clinical trial, restrictive inclusion criteria make it difficult to generalize their results to “real-world” populations. Patients seen in clinical practice are likely to be in worse conditions than those who meet RCT because severe symptoms, comorbidity, and/or acute suicidality are often exclusion criteria for RCT (27). Therefore, it is unclear how the group of severely depressed patients (in fact, those who should receive ATD) will respond to them.

Meta-analyses deal with other difficulties and limitations. Outcome measures may not meet inclusion criteria and, therefore, keep excluded from the meta-analysis. Negative studies are also less likely to be published and hence are not available.

Despite all these methodological limitations, available data suggest that efficacy is not uniform among antidepressants. In any case, selective serotonin reuptake inhibitors (SSRIs), as a group, have proven to be the most effective agents in reducing depressive symptoms in children over 12 years.

In a meta-analysis conducted by Bridge et al (24), that included 15 RCT assessing effectiveness of SSRIs in child and adolescent depression, the estimated Number Needed to Treat to Benefit (NNTB) for the group was 10, meaning that for every ten youths given an SSRIs instead of placebo for the treatment of depressive symptoms, one would experience improvement.

According to the 2009 Cochrane Systematic Review (27), there are marked differences in efficacy among SSRIs. Clinical trials with fluoxetine have provided the most consistent evidences of effectiveness reducing depression symptoms in both children and adolescents (21, 28, 29). The Treatment for Adolescent Depression Study (TADS) estimated that the NNTB with fluoxetine was 4–6 (30). Fluoxetine is the only SSRIs that has proven efficacy in children younger than 12 years. It also has the best risk/benefit ratio (18, 31, 32). These optimal results with fluoxetine may be due to the fact that some of these trials included a placebo washout and selected more persistently depressed patients resulting in a lower placebo response (21, 33). With regard to other SSRIs, paroxetine has not proven to be better than placebo and has a worse risk/benefit ratio compared to other ATD. There are no consistent data about the risk/benefit ratio of escitalopram, citalopram, and sertraline (21, 33).

With regard to tricyclic ATD, in 2010 a Cochrane Review on the use of tricyclic drugs for depression in children and adolescents, that included 13 trials, did not find an overall improvement of tricyclic ATD versus placebo for children and adolescents (34). However, it suggested some benefit of ATD versus placebo in reducing symptoms among adolescents. The effect was moderate and of questionable clinical importance. Besides, treatment with tricyclic antidepressant caused more vertigo, orthostatic hypotension, tremor, and dry mouth than did placebo. Its use is not supported by clinical guidelines due to the uncomfortable side-effects/benefit profile (17).

There has also been great debate over the efficacy of psychological versus pharmacological approaches in adolescent MDD. The TADS assessed efficacy of fluoxetine,

CBT, and the combination of both, compared to placebo. After 12 weeks of treatment, CBT alone was less effective than the combination of fluoxetine with CBT or fluoxetine alone, with response rates of 71% for combined fluoxetine plus CBT, 61% for fluoxetine alone, 43% for CBT alone and 34% for placebo (26). However, by week 36, the three active treatments converged (response rates: combined fluoxetine plus CBT 86%, fluoxetine 81%, CBT 81%) (35) suggesting that combined treatment with fluoxetine and CBT significantly accelerates response in adolescent moderate MDD relative to CBT alone or fluoxetine alone. Consequently, clinical guidelines recommend combined treatment as the treatment of choice for moderate-severe major depressive disorder in adolescents (3, 17). However, evidence from other studies does not support this recommendation. The Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT), a pragmatic randomized controlled superiority trial that compared the efficacy of a combination of fluoxetine and CBT together with clinical care versus fluoxetine and clinical care alone in adolescents with moderate to severe major depression, found no evidence of an improved outcome by week 28 with the combination treatment (15). Melvin et al. (36) did not find the combination of CBT and sertraline to be superior to either treatment alone. Contrary to the TADS, in this trial participants receiving CBT alone showed a better acute treatment response than those treated with sertraline alone (odds ratio = 6.86; 95% CI, 1.12–41.82).

Published studies of sufficient design to produce meaningful results on managing resistant MDD in adolescence are also very limited in number. Nonetheless, mention should be made to the Treatment of Resistant Depression in Adolescents (TORDIA) randomized controlled trial. It evaluated the relative efficacy of four treatment strategies in adolescents who continued to have depression despite an adequate initial treatment with an SSRI and that had never received CBT. Treatment strategies were: 1) switch to a second, different SSRI (paroxetine, fluoxetine or citalopram), 2) switch to a different SSRI plus CBT, 3) switch to venlafaxine, or 4) switch to venlafaxine plus CBT. The combination of CBT and a switch to another antidepressant showed a higher response rate than a medication switch alone (54.8%; 95% CI, 47%–62% vs. 40.5%; 95% CI 33%–48%). Contrary to the authors' hypotheses, switching to venlafaxine was not superior to switching to another SSRI, but associated more adverse effects. Evidence from this trial supports the choice of another SSRI over venlafaxine as a second-line antidepressant in the treatment of MDD in adolescence (37).

5.4 Safety

Efficacy and safety issues with regard to ATD in children and adolescents have been under debate for the last three decades. Since the early 1990s, questions concerning a possible ATD induced suicidal ideation and behavior (suicidality) in children and adolescents, based on uncontrolled clinical observations, were raised. These concerns reappeared in 2003 based on data from some RCT. The British Committee on Safety of Medicines (CSM) decided to undertake a comparison of published and unpublished data

on the risk and benefits of these drugs for the treatment of child and adolescent MDD. The meta-analysis concluded that, although available published data at that point suggested a positive risk-benefit profile for some SSRIs, the risk could outweigh the benefits of these drugs (except for fluoxetine) when unpublished data were considered (32). That is the reason why, in June 2003, the British Medicines and Healthcare Products Regulatory Agency (MHRA) released a statement contraindicating the use of paroxetine and venlafaxine in this context. Soon, this contraindication was extended to the use of all SSRIs other than fluoxetine for patients younger than 18 years with depressive illness.

Simultaneously, the FDA commissioned its review of 24 randomized placebo-controlled trials assessing use of ATDs in the treatment MDD, anxiety disorders and of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents (38). It concluded that the use of antidepressant drugs in that population was associated with a modestly increased risk of suicidality with an overall risk ratio for SSRIs in depression trials of 1.66 (95% CI, 1.02–2.68). There were no completed suicides in any of these trials among the approximately 4,600 patients evaluated, but this sample was not large enough to detect such an effect. After that report, the FDA modified antidepressant drug labeling to include a boxed warning of this risk. However, the FDA did not contraindicate any of the antidepressant drugs for pediatric use. Instead, it encouraged prescribers to balance this risk with the clinical need and to closely monitor patients as a way of managing the risk of suicidality. An update was published in 2007, including data from 2 large clinical trials of pediatric MDD (22, 24, 26). It reported a 3% (95% CI, 2–4%) pooled absolute rate of suicidal ideation/suicide attempt in antidepressant-treated MDD participants and 2% (95% CI, 1–2%) in those receiving placebo. The pooled risk difference was 1% (95% CI, –0.1–2%) estimating that the Number Needed to Harm (NNT) was 112 (24). Therefore, they found evidence of an overall small but increased risk of treatment-emergent suicidal ideation/suicide attempt.

Conclusions from these meta-analyses keep in line with a recent Cochrane review on this topic where, after analyzing data from 12 RCT, there was a reported evidence of an increase risk of suicidality for those prescribed SSRIs ($R^2 = 1.80$, 95% CI, 1.19–2.72) (27).

However, the TADS study that included a systematic assessment of suicidality, found that suicidal ideation improved in the four treatment arms, with greatest improvement in the combined treatment of fluoxetine and CBT (31). However, at the 12-weeks assessment, patients with fluoxetine had more suicide-related events than those with placebo. Results of this large RCT support that suicidality in pediatric MDD, rather than increasing, would decrease with every treatment of MDD but to a lesser extent when treated with SSRIs only, compared to combined treatment of fluoxetine and CBT or CBT alone. It also suggests that CBT can offer some protection against suicidal risk. But other studies on the same topic such as ADAPT do not confirm this findings (15).

There are other data that seem inconsistent with a role for ATD drugs in inducing suicidality in pediatric patients. Introduction of selective serotonin reuptake inhibitors (SSRIs) may have played a crucial role in the reduction of adolescent suicide rates since the 1990s (39). In fact, between 2003 and 2005 youth suicide rates increased

following the reduction of SSRIs prescription after issuing of public health warnings about the possible association between antidepressant use and suicide ideation (40).

In summary, there is enough evidence to support the need of monitoring suicide risk in children and adolescents in treatment with SSRIs. Some authors support the hypothesis of a causative link between ATD and suicide risk in this population but, at the same time, others underline that, when the number of SSRI prescriptions decreased after public health warnings, suicide rates in adolescents increased. Therefore, some confounding factors may intervene in the relation between suicidal behavior and SSRIs that are not taken into account.

5.5 Clinical recommendations

In Table 5.1 we summarize some clinical recommendations when treating children and adolescents with antidepressants.

Table 5.1: Clinical recommendations

Before prescription	<ul style="list-style-type: none"> – Make sure the indication for ATD treatment is correct – Provide complete information to the patient and the family with regard to the objectives, side effects and expected benefits of the treatment – Evaluate and measure the clinical and functional status with validated scales such as the CDRS-R (Children Depression Rating Scale Revised), C-GAS (Children Global Assessment Scale) or the GAF (Global Assessment of Functioning) – Note previous symptomatology such as suicidal ideation and/or anxiety or depressive symptoms – Evaluate previous potential interactions between the ATD and other drugs
Choose the ATD	<ul style="list-style-type: none"> – First line treatment: Fluoxetine – Second line treatment: escitalopram, sertraline, or citalopram – Not recommended: paroxetine, venlafaxine, tricyclics, MAOIs, Hypericum
Dosage	<ul style="list-style-type: none"> – Start with a lower dose (fluoxetine 5–10 mg per day, escitalopram 5 mg per day, citalopram 5–10 mg per day and/or sertraline 25 mg per day) – Start slow and go slow – In adolescents the final dose may be similar to that of adults
Follow-up	<ul style="list-style-type: none"> – Evaluate depressive symptoms every 4 weeks and wait until 6–8 weeks to see if the ATD has been effective – Evaluate global functioning. If clinical improvement is not followed by better functioning, presence of comorbid conditions should be taken into account – Check the patient's and family's adherence to the treatment – Register any side effect and explore suicidal ideation (weekly during the first 4 weeks of treatment)
Duration of treatment	<ul style="list-style-type: none"> – Keep the effective dosage at least 6–12 months after remission – During this maintenance phase, follow-up visits should take place at least once every 1–3 months
Treatment withdrawal	<ul style="list-style-type: none"> – Chose a low stressful period (e.g., vacation) – Go slow (descent in 6–12 weeks)

5.6 Conclusions

Clinical recommendations about ATD use during childhood and adolescence are limited due to the biases on the information about their efficacy and security obtained from RCT. Moreover, differences in the clinical presentation of MDD in these populations as well as in their treatment responses compared to adults challenge the hypothesis of MDD as a homogeneous phenomenon during the human life span.

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6 Suicide prevention in depressed adolescents

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Adolescent depression is a highly prevalent disorder with significant morbidity and suicide mortality. It is simultaneously highly responsive to treatment. Adolescents wish to discuss depression with their providers. Providers routinely receive opportunities to do so. These characteristics of prevalence, morbidity, mortality, responsiveness, and accessibility make adolescent depression an excellent target of care. However, most health care trainees and professionals report low confidence in caring for adolescent depression. As a caregiver community we fare poorly in routine matters of assessment and management of adolescent depression. All health care professions are trained within a medical model. The conceptualization of adolescent depression and suicidality within the medical model may increase provider confidence and performance. Epidemiology and neurobiology are presented with emphasis in this review. Legal concerns also affect health care professionals. Providers may deviate from evidence-based medicine owing to anxieties that the identification and treatment of depression may induce suicide and consequent legal culpability. A review of the historical context and relevant outcome trials concerning the increased risk of suicidality in depressed adolescents treated with selective-serotonin reuptake inhibitors (SSRIs) may increase provider comfort. Increased didactic and experiential training improve provider performance. Proven models are presented, and the testable hypothesis is presented that education which incorporates the views of this article will produce the best care for depressed adolescents.

6.1 Introduction

Adolescent depression is relevant to a wide range health care trainees and providers. Depression affects about 1 in 6 American female adolescents and 1 in 12 males (1). At least a quarter of these adolescents will go on to have problems with their families and friends, half will drop out of school, and a third will end up involved with the police or court system (2). Over half of these adolescents will attempt suicide (3).

Providers have both the means and the opportunity to address this disorder. Adolescent depression is highly responsive to treatment, and struggling adolescents want care. Help with handling stress and depression are two of the top three topics most frequently requested of their internists, pediatricians, and family practitioners (4).

Unfortunately, clinicians are not sufficiently trained about adolescent depression and suicidality. Primary care providers correctly identify less than a fourth of youth with a depressive or anxiety disorder (5). Whereas 64% and 53% of primary care providers report routinely screening for adolescent depression and suicidal

thoughts, respectively, only 16% and 7% of their patients reported receiving these services at their last visit (6). The inability to detect depressed adolescents hinders suicide screening practices and prevention. If providers fail to identify at-risk depressed youth, the sole opportunity for suicide prevention may be missed.

Evidence suggests that trainees (7) and professionals (8) are interested in receiving additional training. In one study, over half (64%) of American pediatric residency directors report perceiving that their program's training about depression and suicide was inadequate (9). Individuals and institutions both appear open to targeted training. Self-perception as sufficiently trained translates into improved real-world practice (7).

All health care professions are trained within a medical model. Training may improve provider confidence by emphasizing the epidemiology and neurobiology to place the disorder within a familiar conceptual context. Patient suicide is a highly emotionally-charged fear of most providers. This fear is complicated by recent concerns that effective depression treatment may induce suicidality in adolescents. Legal factors compound the fear (10). Training should highlight the historical outcome trial data behind these concerns to advance rational processing and care.

We believe that the emphasis of the medical model is crucial to provider education in the care for adolescent depression and suicide. Effective training methods have been empirically proven. We review the data to convey models by which these two concepts may be effectively taught.

6.2 Adolescence as a phase of human development

The importance of care provision in adolescence begins with an understanding of its biological context. Brain changes during adolescence are not just an extension of childhood development. Adolescence marks a new developmental phase (11).

Grossly anatomic, histologic, cellular, enzymatic, and neurochemical changes proceed in the brain. Non-linear and region-specific reductions in cortical volume occur (12). These are accompanied by increases in white matter density, increases in axonal diameter and myelination, and synaptic pruning (13). Developmental transformations in neuronal circuitry are associated with prefrontal cortex under-recruitment in adolescents compared to adults (11). Amygdala activation in response to emotional cues is exaggerated as compared to both children and adults. A net effect of increased dopaminergic input to the prefrontal cortex (PFC) and a subsequent shift in the balance between subcortical and cortical dopaminergic drive dominance occurs (11). The increased capacity for understanding and responding to social, emotional, and interpersonal cues characteristic of adolescence results from these changes to biochemical foundation of adolescent experience.

6.3 Depression in adolescence

The importance of the problem

The high prevalence, morbidity, mortality, accessibility, and treatment responsiveness of adolescent depression make it an ideal target of care. Treatment of depression additionally addresses comorbid psychiatric disorders. These include substance use disorders, eating disorders, and delinquent behavior. These comorbidities are often poorly responsive to psychopharmacological treatment, and the treatment of comorbid depression is often the first-line treatment for these disorders. Depression serves as the gateway for addressing a wide range of psychiatric disorders in adolescence.

Depression is also highly comorbid with multiple problems prevalent in primary care that are typically characterized as non-psychiatric. These include problems such as obesity (14) and smoking (15). All providers are sensitively aware to the significant morbidity and mortality of these conditions, including diabetes and cancer. Effective treatment of adolescent depression is a crucial skill for all providers to improve multiple domains of adolescent health.

Epidemiology and prevalence

Depression surges in adolescence. The prevalence of depression is approximately 1% in children (16). This raises to a point prevalence of 5% and a lifetime prevalence as high as 25% by late adolescence (17). Concurrent with this surge is the development of a gender gap. Depression afflicts female and male children equally. In contrast, a 2:1 female predominance develops during adolescence. This ratio persists through adulthood and is associated with pubertal status rather than chronologic age (18).

Psychiatric comorbidity is present in as much as two thirds youth with depression (19, 20). Two or more disorders are comorbid in about one in eight. Frequent disorders are dysthymia and anxiety disorders, disruptive disorders, and substance use disorders (19). Depression is additionally a risk factor for persisting conditions traditionally characterized as non-psychiatric, such as obesity (21). Comorbidity conversely influences depression: the greater the comorbidity, the greater the likelihood of parental conflict, suicide attempts, and functional impairment (22).

6.3.1 Neurobiology of adolescent depression

Biological context renders vulnerability to depression. Two key neuronal circuits are implicated in models of adolescent depression. Limbic system circuitry which connects the ventral prefrontal cortex and the amygdala, hippocampus, and HPA axis is overactivated in depression (23). In contrast, reward system circuitry connecting the prefrontal cortex, striatum, and ventral tegmental dopamine neurons is underactive in depression (24, 25).

Brain-Derived Neurotrophic Factor (BDNF), a growth factor which supports neuronal survival and synaptic plasticity, is implicated in the development of such circuits (26) and thus in adolescent depression (27). It is also associated with suicidal behavior (28). Adolescent-onset depression is associated with a specific genotype in this growth factor (29, 30). Sex hormones also influence neuronal circuit organization (31). The surge of female depression at puberty suggests that sex hormones may contribute to organizational configurations associated with depression. Sex hormones may also exert direct effects upon circuit components; for example, estrogen promotes stress-induced prefrontal cortex dysfunction (32).

The serotonergic system is the target of the first line treatment for both adolescent and adult depression. Dysfunction in this system has long been implicated in depression. Particular genetic variants within the system are associated with depression when exposed to stressors. With over 50 dedicated studies and several meta-analyses (33), the best researched genetic variant is the serotonin transporter allele (5-HTTLPR) (34). The strongest evidence for this association may exist in the adolescent population when gender and additional genetic variants are accounted for (35).

Models of adolescent depression extend beyond the brain. The hypothalamic-pituitary-adrenal (HPA) axis shows dysfunction in adolescent depression (36). Chronically elevated corticosteroid concentrations impair serotonergic neurotransmission (37). Transversely, serotonergic abnormalities impair HPA function: Newborns with 5-HTTLPR portray higher HPA activation in response to stress (38). In the future measures of the HPA axis functionality may serve as a biomarker for depression.

6.3.2 Treatment

Depression is a heterogenous disorder for which guidelines recommend a stratified treatment approach (39). Mild depression may be initially treated through education, support, and case management related to school and family stressors. More complicated depression, or mild depression which does not resolve through the above interventions within 4–6 weeks, merit structured psychotherapy and/or medication management.

Multiple psychotherapy modalities have been applied to adolescent depression. No modality has ever been shown to be significantly more efficacious for the depressed adolescents as a whole. Though about 80% of published trials have tested Cognitive Behavioral Therapy (CBT) and a sizeable evidence basis has accumulated supporting this modality (40), the process of choosing a psychotherapy should be tailored to the individual adolescent. For example, pronounced family conflict may indicate family-based therapy (FBT), or social isolation may indicate interpersonal therapy (IPT). A comprehensive review of psychotherapy for adolescent depression is beyond the scope of this paper, though particular therapies will be referenced where applicable.

Medication management may be used alone or in combination with psychotherapy. To date, only fluoxetine (age 8+) and escitalopram (age 12+) are FDA-approved for the treatment of adolescent depression. The historical context, as has been reviewed elsewhere (41, 42), merits summary.

Though fluoxetine was first commercially available in December of 1987, it was not until 1997 that the first positive randomized controlled trial in children and adolescents with MDD was published (43). Practice parameters which recommended the Selective Serotonin Reuptake Inhibitors (SSRIs) as initial therapy were published the following year (44), and within 4 years the use of antidepressants at the index visit of a new episode of depression in adolescents jumped from 5% to nearly 40% (45). The FDA approved fluoxetine for the treatment of childhood depression in 2003 following a second positive randomized trial (43). Escitalopram would follow in 2009 (46).

Two pivotal trials were published in the interim. These trials were the Treatment for Adolescents with Depression Study (TADS) (47) and the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) (48). TADS found no significant difference between response rates to CBT, fluoxetine treatment, and combined fluoxetine treatment with CBT in a group of depressed adolescents randomized to these treatments after 24 weeks of treatment. Benefits were sustained at 1-year follow-up (49). However, combination treatment showed the shortest time to response, was most cost-effective (50), and had significant impact upon suicidality rates. TORDIA studied depressed adolescents who had failed a prior SSRI and were randomized to switch to either a second SSRI, a second SSRI with CBT, venlafaxine, or venlafaxine combined with CBT. TORDIA found higher response rates with combination therapy. This may reflect the greater prevalence of comorbid environmental and psychological conditions in this SSRI-resistant population as compared to that of the TADS. A greater incidence of adverse effects in venlafaxine treatment cemented combination therapy with an SSRI as the current optimal treatment strategy for depressed adolescents.

6.3.3 Suicidality in depressed adolescents

The importance of the problem

The preceding discussions of depression morbidity and treatment response have neglected its association with suicidality. Suicidality is a broad term which encompasses suicidal ideation, suicide attempts, and suicide. Suicidal ideation and attempts are both risk factors for adolescent suicide (51). Suicide is the ultimate consequence of adolescent depression. Repercussions extend beyond the individual. Affected families will experience defined responses including psychological shock, self-reproach, social stigmatization (52). Suicide additionally clusters, and the death of one adolescent can propagate without adequate postvention care (53).

Epidemiology and prevalence

Suicide is the third leading cause of adolescent death in the United States (54). Globally, it ranks second (55). For every American adolescent suicide there are 100 to 200 suicide attempts (56). About 1 in 15 American high school students reported having attempted suicide in 2009, and over twice that many (13.8%) reported having suicidal thoughts within the previous year (57).

The adolescent suicide rate slowly increased through most of the 20th century (58). In the US, a youth rate of just under 10 per 100,000 in 1970 had increased to almost 15 per 100,000 by the mid 1990s. Subsequently, the suicide rate began to decline. In the US, the rate returned to just over 10 per 100,000 by the early 2000s (59); similar declines occurred in Australia (60), Canada (61), and select European countries (62). American data now show that this decline was temporary (63).

Age, sex, and country-specific variables effect suicide rates and methodology. Despite an increased frequency of suicide attempts among female adolescents, male suicide rates are generally two to six times higher than that of females (64). This difference is attributable to the greater average lethality of male suicidal behavior. Males are more likely to use firearms than their female peers; in the US and in some European countries such as Switzerland where firearm ownership is high, suicide by firearm is significant (57% and 27% of suicides, respectively) (65). Hanging is another highly prevalent and lethal method which is less amenable to means restriction prevention measures; new data show its incidence may be increasing (66).

Relation of adolescent suicidality to depression and comorbid conditions

Depression is the strongest risk factor for suicide among the adolescent psychiatric disorders. Depression raises the risk of a suicide attempt by a factor of 12 in boys and 15 in girls (67). Over half of suicide victims are diagnosed with depression at the time of death (68).

Comorbid disorders, including anxiety, substance use, and disruptive behavior disorders, all increase suicidality risk (22). The alcohol use disorders, particularly in older male adolescents, impart significant risk of suicidality. Comorbidity between depression and alcohol abuse is as high as 73% in adolescent populations (69). Alcohol use predisposes to impulsivity and aggression. Both these traits contribute to elevated suicide risk.

The comorbidity of Post-Traumatic Stress Disorder and Major Depressive Disorder is also significant. Neurobiological evidence suggests that some or all individuals with this comorbidity have a separate psychobiological condition which is termed Post-Traumatic Mood Disorder (PTMD) (70). Adolescents with PTMD have a higher risk of suicidality than expected with separate diagnoses of either PTMD or PTSD (71).

6.3.4 Relation of adolescent suicidality to medications (SSRIs) which are frequently used to treat depression

Reports of increased suicidality in individuals treated with SSRIs began shortly after fluoxetine's commercial introduction in 1987 (72, 73). In adults, the first pooled data analysis of suicidality found a decreased risk of suicidality in adults treated with SSRIs (74). A subsequent 2003 review found no statistically significant risk increase or decrease among treated adults (75).

The same year saw the first FDA approval of an SSRI for childhood depression. A series of reports in *The Guardian*, as well as two BBC television documentaries, preceded a warning from the British Department of Health that a review of both unpublished and published proprietary data found an increased risk of suicidality in adolescents treated with paroxetine. The FDA convened a review of 24 controlled clinical trials of nine antidepressants which found a 4% risk of suicidality with SSRI compared to a 2% risk with placebo (76). The well-known “black box” warning ensued in October of 2004. Its age range of concern was subsequently (May 2007) extended to young adults up to 24 years of age. Increased media attention and governmental actions globally, including a similar precautionary notice from the Japanese Ministry of Health, followed (77).

Following the black box warning, prescription rates fell (78). A simultaneous increase in the national suicide rate among adolescents was observed; concern for a causal relationship was expressed (63). A persisting decrease in the diagnosis of adolescent depression occurred (78, 79). The decrease in antidepressant prescriptions was not accompanied by an increase in non-pharmacologic treatments, such as psychotherapy. Though causation is only implied, these findings suggest the black box warnings have had unintended consequences. Simultaneously, it may have prevented some suicides. Additional studies are needed.

What do we know today of the risk of suicidality in adolescents treated with SSRIs? First, as we have known since the original FDA review, there is no evidence supporting an increased suicide rate among adolescents treated with SSRIs. There is only an increase in the rate of suicidal ideation and behavior, such as suicide attempts. Epidemiological data, though devoid of causal implications, may support treating depressed adolescents. Multiple studies have suggested that the late 20th century reversal of the gradually rising adolescent suicide rate was attributable to the increase in use of SSRIs in depressed adolescents (80, 81). The return to a rising suicide rate following the FDA advisory and subsequent decrease in SSRI prescriptions has elicited great concern of causation and may support the targeted use of SSRIs in this population (63).

Additionally, TADS found that CBT erased the increased suicidality risk. Psychotherapy may be key. However, this protective response was not replicated in TORDIA. This differential finding may be related to population differences between the two studies.

Data will continue to accumulate. For example, a recent study which used person-level data from four youth trials failed to find any increased suicidality risk

(82). Until then, a comfortable knowledge of the data will allow fact-based optimized care tailored the individual adolescent.

Future neurobiological research and developments will improve individualized care. Pharmacogenetics, already an established field of study within adolescent depression (83), will enable biologically-customized pharmacotherapy. Biomarkers will serve similarly. Biomarkers are objective measures associated with clinical disorders that ideally simultaneously serve as the target of reparative interventions (84). Endophenotypes are heuristic intermediaries between upstream genotype products and clinical phenotypes which have already been developed in studies of depression (85) and suicidality (86). These reliable, objective neurobiological methods will increasingly gain clinical relevance.

6.4 Education of health care trainees and professionals

Recognition of depression in adolescents in psychiatric and primary care

Both primary care (87) and mental health (88) providers under-recognize adolescent depression. Primary care providers recognize depression or anxiety in just under a third of diagnosable cases (5). Several factors may contribute to low recognition. Chiefly, adolescents often enact rather than verbalize the negative affect of depression. As only 56% of pediatricians report that they usually require about depression (89), the topic may indeed not be verbalized by either party. Somatic symptoms, functional impairment, behavioral problems, and sleep and appetite disturbances may replace direct verbalization of affect in the adolescent. The high prevalence of comorbidity in depression may distract from depression as a treatment-responsive disorder warranting first line intervention.

It is our opinion that medical provider discomfort with depression in adolescents may predispose providers to focus preventative efforts elsewhere. Grounding adolescent depression within a neurobiological medical model may increase provider comfort and subsequent recognition.

Recognition of suicidality in adolescents in psychiatric and primary care

Suicidal ideation is similarly withheld if not directly assessed (90). Direct questioning revealed a suicidal ideation preceding two-week prevalence of 22% preceding two-week incidence among adolescents who presented to their primary care provider without any psychiatric complaints (91).

As in adults, there is no evidence of iatrogenic effects of suicide screening in adolescence (92). The straightest path to increased recognition of adolescent suicidality is simply to ask. Direct questioning, simple empathic support, and attentiveness yield the greatest rates of emotional and behavioral disclosure from adolescents and their parents (93, 94). Reducing adolescent access to firearms and assessing for

past attempts or future plans of suffocation will appropriately target resources to adolescents with the highest risk of suicide completion.

Management of depression and suicidality in adolescents in psychiatric and primary care

Psychotherapy referral with or without medication management is a promising alternative. As aforementioned, TADS found that the addition of CBT to medication management erased the increased suicide risk. There is increasing evidence for psychotherapy, in particular family-based interventions (95). For example, Attachment-based family therapy (ABFT), was developed to reduce depression and suicidal ideation (96). It was recently shown in a randomized controlled trial to be more efficacious than community care in reducing depression and suicidality (97).

Fear of inducing or being powerless to prevent adolescent suicidality may predispose providers to under-recognize both suicidality and depression in adolescents. Evidence-based emphasis upon trial-outcome data will dispel myths, raise provider confidence, and contribute to greater recognition and treatment rates.

6.4.1 How to teach health care trainees and professionals to recognize and manage adolescent depression and suicidality in adolescents in psychiatric and primary care?

All providers should feel comfortable attending to suicidality in depressed adolescents. A sizeable (45%) proportion of non-specialist emergency room providers do not agree that screening is important; in fact, 70% support screening only when the chief complaint is psychiatric (98). We believe training must first address this prevalent provider belief and its underlying factors prior to instruction in more complex screening and management algorithms.

Over 40,000 individuals have participated in the twelve suicide workshops for mental health providers described in the literature (99). Many others have engaged in the greater number of trainings for non-specialist providers (100). These programs share common features. Didactics are often supplemented by the use of a standardized patient. The use of these two strategies together are associated with greater training outcomes than the use of either alone (7). Video demonstration training increases provider confidence in discussing mental health concerns within pediatric populations. Web-based educational programs are also commonly employed.

Increased knowledge of the neurobiological context of adolescence, the epidemiology and prevalence of adolescent depression and suicide, and treatment implications with a focus on the SSRIs will increase provider comfort in addressing these important issues. Increased comfort and the perception of receiving adequate training will translate into improved screening and management practices (8).

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Section III: **Violence and abuse**

7 Child sexual abuse and suicide in adolescents and adults

Betsy S. O'Brien and Leo Sher

Child Sexual Abuse (CSA) is widespread and is associated with various psychopathology, including Axis I and II disorders, maladaptive and impulsive behaviors, and suicidal behavior in adolescence and adults. The pathophysiology of this association is not well understood. However, it is clear that suicidal behavior in individuals with a history of CSA is a significant social and medical problem warranting further investigation. **Methods:** An electronic search of the major behavioral science databases (limited to the most recent studies in the last 20 years) was conducted to retrieve studies detailing the social, epidemiological, and clinical characteristics of child sexual trauma and their relation to suicidal behavior in adolescents and adults. **Results:** Studies indicate that child sexual abuse is related to an increase in Axis I and II diagnoses including depression, PTSD, conduct disorders, eating disorders, alcohol and drug abuse, panic disorders, and borderline personality disorder. CSA is also related to an increase in impulsivity and risky behaviors. CSA has been linked to an increase in suicidality as well. CSA makes both direct and indirect contributions to suicidal behavior. It is a complex process involving multiple variables that include psychopathology, maladaptive personality features, as well as the direct contribution of CSA itself. Psychopathologies such as mood and personality disorders and impulsivity may modulate the relationship between CSA and suicidal behavior. Some preventive measures for decreasing the prevalence of child sexual abuse and suicidality may include education as well as increasing access to mental health services.

7.1 Introduction

Due to the differences between the assessment tools used to conceptualize Child Sexual Abuse, there is a lot of variability in what is included in the definition of CSA (1, 2). Some sources, for example, include rape or attempted rape in their definition of CSA, whereas other sources also include contact abuse (fondling) and non-contact abusive experiences, such as genital exposure. The age criterion also varies between different sources, with some investigators claiming that 16 should be the cut off age, while others propose to increase this arbitrary set limit to 18 years (1, 2).

The data on the prevalence of CSA also contains tremendous variability, partly due to the differences in the definitions of CSA, underestimation due to the retrospective nature of recall studies and variance in sampling methods and data collection (1). Vogeltanz et al (1, 3) used the Wyatt Criteria, which defines CSA as an intrafamilial sexual activity before the age of 18 years that was unwanted, or that involved a family member 5 or more years older than the respondent; and any extrafamilial sexual

activity that occurred before age of 18 and that was unwanted or that occurred before age of 13 years and involved another person 5 or more years older than the respondent (1, 3). Vogeltanz and colleagues (1, 4) estimated CSA prevalence in women to be 21–32% using the most inclusive definition of child sexual abuse, and 15–26% using a less inclusive criterion (1). Emphasizing the variability that exists in the estimated prevalence of CSA, Laaksonen and colleagues reported a CSA prevalence of 1.8–7.5% versus 15–26% reported by Vogeltanz and colleagues (1, 4). Laaksonen and colleagues estimated prevalence comes from a sample of 13,000 responders to the Childhood trauma Questionnaire (4), the disparity in estimated prevalence of CSA between Vogeltanz and colleagues and Laaksonen and colleagues may reflect a difference in their definition of CSA or some variance in sampling methods and data collection. The disparity may also reflect a true decline in CSA prevalence in the 10 years between the two publications as Laaksonen and colleagues suggested in their paper (1, 4).

Although there seems to be some variability in the definition of child sexual abuse and its prevalence, numerous studies have consistently demonstrated that child sexual abuse is widespread and is associated with a spectrum of psychiatric conditions and maladaptive behaviors including higher risk of intimate partner violence, more permissive and less effective parenting behaviors, Axis I diagnoses such as depression, PTSD, bipolar disorder, Axis II diagnoses such as borderline personality disorder, as well as risky sexual and suicidal behaviors (5–10).

7.1.1 Literature search

An electronic search of the major behavioral science databases (PUBMED, PSYCINFO, MEDLINE) was conducted to retrieve studies between the years of 1990–2012 detailing the social, epidemiological, and clinical characteristics of psychological trauma in female adolescents and their relationships to behavior. Search terms included “child abuse,” “childhood trauma,” “sexual abuse,” “suicidal behavior,” “suicidal ideation,” and “suicide attempt.” Additional references were incorporated from the bibliographies of the retrieved articles.

7.2 Child sexual abuse and psychopathology associated with suicidal behavior

Sexual abuse and trauma in childhood and adolescents is associated with a higher lifetime prevalence of psychopathology, both Axis I and II disorders, as well as pathologic behaviors (5–9). Axis I disorders associated with CSA include PTSD, depression, conduct disorder, panic disorders, alcohol and drug abuse, and eating disorders (11, 12). Associated Axis II disorders include Borderline Personality Disorder, Paranoid,

and Antisocial Personality Disorder (13, 14). Even when the factor of a formal Axis I or II diagnosis is controlled for, sexual abuse and trauma in childhood and adolescents is associated with higher rates of psychiatric symptoms including depressed mood, impairing experience of loneliness, feelings of being overweight and poor body image and increased risk of conduct behavior including shoplifting, theft, and vandalism (15).

Additionally, CSA can modify the onset and trajectory of psychopathology. Numerous investigators have shown that CSA is associated with an earlier onset of psychiatric disorders and symptoms and may worsen the severity of Axis I and II disorders. Zanarini and colleagues found that severe CSA worsens the severity of BPD in the core sectors of the disorder including affect, cognition, impulsivity, and disturbed interpersonal relationships (16). Other studies have also found correlation between CSA and borderline personality symptomatology (17). CSA has been correlated with an increase utilization of psychotropic medications (15, 17, 18). CSA has also been correlated with increased utilization of health care including increased telephone contacts to health care facilities, physician visits, ongoing and acute prescriptions, and specialist referral (17).

7.3 Child sexual abuse and impulsivity

Child sexual abuse has also been linked with development of impulsivity and impulsive behaviors (14, 19–21). Braquehais et al (14) defined impulsivity as a spectrum of behaviors that is characterized by an immediate, unplanned response to internal and external stimuli and can include high risk sexual behavior and violence (14). Examples of high risk sexual behavior include engaging in unprotected sex, having more than one partner, sex with a stranger, engaging in anal intercourse, and having an STD (9, 15). CSA is also associated with an increase in violence. Female adolescents who suffered from CSA report higher violence perpetuation (9). Furthermore, child sexual abuse sets a tone for continuation of violence in intimate partner relationships. Studies have shown that females who suffer from CSA are more likely to become the victims of intimate partner violence as adults and more likely to perpetuate violence (9, 22).

7.4 Sexual abuse and suicide

Perhaps the most devastating outcome of the association between sexual abuse and trauma is the increased risk of suicidal behavior. Although the most important risk factor for completed suicide continues to be prior suicide attempt (21, 23), much of the literature identifies CSA as another major risk factor for suicidal behavior in adults

and young adults (10, 11, 18, 21, 24–26). Molnar and colleagues used multivariate discrete time event survival analysis to generate models to calculate the attributable risk of child sexual abuse to suicidal behavior (7). They found that by controlling for the effects of other adversities towards the respondent such as verbal and physical abuse, verbal and physical abuse of parents towards each other, substance problems in mother and father, and attempts or completed suicides by either parent, the risk of suicidal behaviors that could be prevented by removing the factor of CSA, specifically in women, was 11–14.5% (7). Although this study looked at suicidal behavior in a population of 15–54 who had experienced CSA, the study found that the highest probability of first suicide attempts in the females in this population was during adolescence between ages 14–19 years (15). In another study, Ystgaard and colleagues have looked at a population of adolescents in a psychiatric hospital who had made a suicide attempt (24). They found that the prevalence of repeated sexual abuse amongst this population of patients who have made a suicide attempt was higher than the reported sexual abuse in the general population (24).

The nature and pattern of the suicidal behavior have also been shown to be related to history of prior child sexual abuse. Studies have found that people who suffered from child sexual abuse have increased prevalence and severity of repeated suicide attempts (11, 13, 16). Not only does sexual abuse increase the prevalence of suicidal behavior, but it also increases the prevalence of non-suicidal self-injury (NSSI), a risk factor for suicidal behavior, such as cutting, burning, biting, hitting, ingesting non-food, skin picking, and placing objects under skin (25, 27).

Child sexual abuse further increases suicidal risk in patients who have Axis I and II disorders or high impulsivity that independently raises the risk for suicidal behavior. For example, Fergusson and colleagues in looking for factors that distinguish those patients who have depression and develop suicidal behavior from those that don't, found that in addition to being a risk factor for depression, CSA appeared to make patients with depression more vulnerable to suicidal thoughts (28). Carballo and colleagues found that in patients with another Axis I disorder, Bipolar Disorder, a personal history of childhood abuse including sexual abuse and a family history of suicidal behavior increased prevalence of suicidal behavior (29). Similarly, in patients with PTSD, child sexual abuse appears to be responsible, at least partially, for the relationship between its symptoms and suicidal behavior (30). Studies have also shown child sexual abuse has also been associated with increased suicidal behavior in patients with pathologic impulsivity (14).

7.5 CSA and adolescent suicidality

Adolescent suicidality is a significant medical and social problem that warrants special investigation. Sources report that 9.7% of adolescents have attempted to take their own lives at some point and 29.9% have experienced suicidal ideation

(31). CSA is linked to suicidal behavior in young adults and adolescents specifically as well as adults. Evans and colleagues investigated risk factors for suicidality in adolescents and identified multiple sources and using multivariate analyses demonstrated a correlation between child sexual abuse and suicidal phenomena in adolescents (31). Evans et al also demonstrated a correlation between suicidal behavior and other Axis I and II pathology in adolescents including depression, eating disorders and body image in female adolescents, recreational drugs and drinking, and antisocial behaviors (32). Evans et al concluded that the association between CSA and suicidal ideation and behavior in adolescents appears to be a direct association, although certainly other factors such as self-esteem and Axis I and II pathologies may mediate this relationship (32). Bruffaerts et al also found a correlation between sexual abuse and onset and persistence of suicidal behavior in adolescents even when adjusting for the mental health of the adolescent (33). Furthermore, Bruffaerts et al suggest that the correlation between child sexual abuse and suicidal behavior is most pronounced during adolescents especially in regard to actual suicide attempts whereas the correlation between suicide attempts and CSA becomes less strong in adulthood (33).

7.6 Discussion

The relationship between suicidal behavior and sexual abuse is clearly multifactorial. While there is a clearly established relationship between sexual abuse and suicidal behavior in both adolescents and adults, the pathophysiology of this relationship warrants further exploration.

Psychopathology as a mediator between CSA and suicidal behavior

Psychopathology may mediate the relationship between CSA and suicidal behavior. Patients who suffer from Axis I pathology including PTSD, Depression, and Bipolar Disorder as well as Axis II pathology including Antisocial, Borderline, and Paranoid Personality Disorders have an increased risk of suicidal behavior (14, 34–37). CSA also increases the risk for the development of Axis I and II pathologies including PTSD, Depression, Eating Disorders, Substance Disorders, and Borderline Personality Disorder in both adolescents and adults (7, 12, 13, 36). Patients with these disorders and a history of CSA are more likely to engage in suicidal behavior (29, 30, 35, 37), thereby CSA may be a risk factor for the development of psychopathology and it is the presence of psychopathology that may mediate the link between CSA and suicidal behavior.

Impulsivity as a mediator between CSA and suicidal behavior

Child sexual abuse is associated with the development of pathologic impulsivity and with psychiatric disorders including antisocial personality disorder and

substance dependence that are associated with impulsivity (14, 19). Pathologic impulsivity is also associated with an increased risk of suicidal behavior (14, 19). Pathologic impulsivity can include behaviors associated with violence, eating disorders, substance abuse disorders, gambling, and risky sexual behavior (19). As suggested by other sources (14), child sexual abuse may increase impulsive behavior and the presence of impulsivity may mediate the relationship between CSA and sexual abuse.

CSA as an independent risk factor for suicidal behavior

Child sexual abuse may also be an independent variable that directly increases the risk of suicidal behavior. Molnar and colleagues found that even when controlling for other adversities, patients who suffered from child sexual abuse were more likely to go on to develop suicidal behavior in adolescence and adulthood (10). Even when controlling for Axis I and II pathology, studies have shown at least some increased risk of suicidal behavior in adult and young adult patients who have suffered from CSA (26, 36).

Overall, CSA makes both direct and indirect contributions to suicidal behavior. It is a complex process involving multiple variables that include psychopathology, maladaptive personality features, as well as the direct contribution of CSA itself.

CSA and prevention of suicidal behavior

Improving education of the general population, medical community, mental health providers, and gatekeepers may help to mobilize earlier interventions that address these risk factors may improve outcome as measured by decreased child sexual abuse and suicidal behavior (38).

Increase access to care including emergency, medical, and mental health services may improve outcome. It is important to increase and improve emergency room care of sexual assault needs including availability of toxicology, pregnancy tests, and training of health care workers to perform HEADSS (home, education, activities, drug use and abuse, sexuality, and suicidality and depression) assessment in every case suspected to have involved child sexual trauma and abuse (39). Improving access to mental health resources for patients with psychopathology and child sexual abuse including access to multimodal therapy such as dynamic psychotherapy, CBT, DBT for suicidal behavior, and psychopharmacologic treatment may improve outcome (38, 40).

Studies have suggested a role for the education of gatekeepers (38). These studies have proposed a more formal role for gatekeepers who may formally mediate access to care (38).

In summary, a link exists between child sexual abuse and adverse outcomes including development of psychopathology, impulsivity, and suicidal behavior. However, the pathophysiology of this relationship is complex and determining measures to prevent CSA and suicidal behavior warrants a multifactorial approach.

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8 Improving future physicians' responses to adolescent maltreatment

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The purpose of this chapter was to examine the effects of training first year medical students using a Child Advocacy Studies Training (CAST) elective course. The 9 month course was taught by a multi-disciplinary group of professionals and addressed prevention, identification, reporting and responding to all forms of child and adolescent maltreatment. It was hypothesized that, relative to students in a comparison group, students who completed the elective would report being significantly more prepared to identify signs of maltreatment, to report a case of suspected maltreatment, and to recommend or secure needed services for a maltreated child or adolescent, more likely to report suspected maltreatment, even if they did not know for sure it happened, and demonstrate improved knowledge in the areas of maltreatment identification and reporting. Results supported all five of the study's hypotheses and indicate that the CAST program may be an effective method of better preparing future physicians to address child and adolescent maltreatment.

8.1 Introduction

Every year, thousands of children and adolescents suffer from the impact of child abuse and neglect in US. Approximately 2,000 children and youths die each year as a result of abuse or neglect (1). There are 9.2 victims per 1,000 children in US (2). Although very young children are the most vulnerable to maltreatment, in a recent survey, 23.5% of maltreatment victims were aged 12–17 years (2). Maltreatment during adolescence has been shown to increase the risk of arrest, delinquency, violence, drug use, internalizing problems, and externalizing problems (3–6).

Among the many types of professionals involved in efforts to prevent and reduce maltreatment are physicians who, because of characteristics of their professional roles and involvement in patient care, have opportunities to address maltreatment on many levels. For example, all physicians in US are required by law to report suspected abuse. Identification of some forms of maltreatment involves medical examinations by physicians. Physicians have important roles involving educating parents about issues such as parenting, child development, and safety that are highly relevant to the prevention of abuse and neglect. Furthermore, physicians are at times called on by courts as expert witnesses. Physicians are also involved in the development and revisions of medical definitions of child and adolescent abuse that are used by courts and policy-makers.

Specialists such as family physicians and pediatricians also have the advantage of a high degree of patient access compared to other professionals. That is, although

many other health professionals are exposed at some point in their career to cases involving abuse and violence, they treat only a small percentage of children and adolescents seeking specialized care. In contrast, most children and youths have contact with a pediatrician or family practitioner; most children in US see such physicians for well-child visits and following illness or injury. Thus, pediatricians and family practitioners are in important positions involving contact with otherwise hard to reach families who may be at risk for child abuse. Furthermore, pediatricians and family practitioners are in key positions for the provision of preventive care. They are often sought by parents and caregivers for advice on parenting and methods to prevent and handle behavior problems. All of these factors, in tandem with physician's ultimate goal of maintaining the safety and welfare of their patients, make physicians important figures in the fight against maltreatment.

There are indications, however, that some physicians are experiencing obstacles to successfully meeting their responsibilities regarding to child and adolescent protection. For example, the vast majority of children and adolescents suspected of being abused are not reported into the system (7, 8). Research indicates that over half of mental health and health care providers do not report all cases of suspected abuse (7, 8) and that impediments to reporting among physicians are associated with lower than optimal rates of reporting (9–11). For example, in a study with 327 primary care clinicians examining mandated reporting of suspected physical abuse (i.e., physicians, nurse practitioners and physician assistants), only 24% of the children considered possibly abused by caregivers were reported by the clinicians. Even more alarming, only 73% of the children and adolescents considered to be likely or very likely abused were reported by the clinicians (10). This explanation has been supported by other research indicating that physicians sometimes do not feel prepared to intervene effectively when faced with cases of child and adolescent maltreatment (8, 9, 11).

Research suggests that limited or poor quality training in maltreatment is a major barrier. Physicians and other health care providers often report having received very little training, if any, on child abuse prevention (9, 12) child and adolescent advocacy, identification of maltreatment and reporting procedures (8). In one study, the following areas of knowledge pertaining to reporting maltreatment were listed by medical professionals as areas of educational need: knowledge about the actual reporting process, their role in the reporting process, and reporting laws (11). Such findings suggest that future physicians may benefit from education regarding not only the identification of child maltreatment, but also on the reporting process and the providers' role in that process. In fact, many medical professionals have expressed a desire for more education in the area of child maltreatment, suggesting that it would increase adherence rates to mandated reporting (13). Further, child protection has explicitly been identified as an area of neglected training in pediatric residency (14).

Experts and professional organizations involved in medical school education have suggested standards for training in child maltreatment. According to

Reece and Jenny (12), “Training for the detection and treatment of medical problems relies on a shared foundation of biomedical knowledge. Similarly, the knowledge of various etiologic theories of child maltreatment is essential for the health care provider to evaluate cases of suspected abuse and neglect. Now here in medical practice is knowledge about the social constructs of a medical condition more necessary than in the evaluation of a child and family for the possibility of child maltreatment.” In the medical school accreditation standards, the Liaison Committee on Medical Education states, “The curriculum of a medical education program must prepare medical students for their role in addressing the medical consequences of common societal problems (e.g., provide instruction in the diagnosis, prevention, appropriate reporting, and treatment of violence and abuse)” (15). Further, the Council on Medical Student Education in Pediatrics (COMSEP), which functions under the auspices of the Association of Medical School Pediatric Department Chairs and works to define and promote exemplary teaching practices in medical student education (16), suggests the following competencies for medical students in the area of child abuse: list characteristics of the history and physical examination that should trigger concern for possible physical, sexual, and psychological abuse and neglect such as inconsistency in the history, unexplained delays in seeking care, injuries with specific patterns or distributions on the body, or injuries incompatible with the child’s development; describe the medical-legal importance of a full, detailed, carefully documented history and physical examination in the evaluation of child abuse; discuss the concurrence of domestic violence and child abuse and describe markers that suggest the occurrence of family violence; describe the unique communication skills required to work with families around issues of maltreatment; summarize the responsibilities of the “mandatory reporter” to identify and report suspected child abuse; know to whom such a report should be made (17).

Although these standards provide important guidance on what medical education in maltreatment should address, such training remains scarce and inconsistent. For example several studies have documented very limited training on child and adolescent abuse prevention and advocacy for emerging medical professionals (8–11, 13, 18, 19). When it does exist, it is often a single offering, separated from the medical curriculum, rather than a coordinated, multifaceted, multi-disciplinary approach (20).

To date, there is not an evidence-based approach to medical training in child and adolescent protection. Although standards exist for medical student training in maltreatment and protection, there is not clear consensus on how to incorporate these objectives into a medical school curriculum, and existing approaches have not been rigorously evaluated (21, 22). Thus, although some researchers and educators have attempted to develop proposed model curricula, the efficacy of such curricula has not been well-tested.

Research suggests that targeted training at the graduate level may be effective (23). Participants in one study involving students and professionals in mental health, for

example, demonstrated improved knowledge of State and Federal laws, improved identification of child and adolescent maltreatment, and improved knowledge of requisite skills involved in reporting suspected maltreatment. In a recent study of a medical student course, medical students' self-reported preparedness to identify and report maltreatment, as well as their likelihood of reporting, improved significantly from just prior to just following the training (24). Although promising, that study suffered from limitations including a very small sample and lack of control group. One additional study examined whether or not training first and second year medical residents in child and adolescent maltreatment issues is effective; this study found a medium effect size for training medical residents in the area of maltreatment (25). Although this study found training medical residents to be efficacious, training efforts can begin much earlier in medical school, thus reaching future physicians who eventually practice in a variety of fields.

Because too little or poor quality training in maltreatment may strictly impair the ability of physicians to meet their responsibilities in the area of child and adolescent protection, it is imperative that evidence-based training be established. The Child Advocacy Studies Training (CAST) program is based on the notion that the large majority of college-educated students eventually will become involved in professions that involve child advocacy (26). The purpose of CAST is to educate future professionals to more effectively prevent, identify, and respond to maltreatment. Through CAST, students in medicine, law, criminal justice, public health, early childhood, computer science, sociology, women's studies, psychology, education, social work, nursing, and other fields are trained in evidence-supported methods of preventing, identifying, and responding to child/adolescent abuse and neglect. Students also are taught how to implement and improve maltreatment prevention and child/adolescent protection systems of care the communities they join after graduation. The CAST program places emphasis on teaching and consultation by a wide variety of professionals in the field (e.g., psychologists, physicians, law enforcement, CPS workers, etc.) to keep the curriculum both current and reality-based. The program utilizes and promotes multi-disciplinary approaches to the problem of child and adolescent maltreatment.

Although the CAST program has been implemented nationally at several universities at the undergraduate and graduate levels, the program has not yet been implemented broadly in medical school settings. However, as reviewed above, physicians can be highly effective educators and leaders in such efforts (12, 14, 27), and use of the CAST program for improving the training of future physicians in maltreatment prevention, intervention and advocacy holds significant promise.

The purpose of the current study was to examine the effects of training medical students using a CAST elective course. It was expected that medical students' self-reported preparedness to address maltreatment and likelihood of reporting suspected maltreatment would increase significantly following CAST training, relative to a comparison group. In addition, it was anticipated that students' knowledge

in the areas of maltreatment identification and reporting would improve relative to comparisons. Specifically, it was hypothesized that:

1. Relative to students in the comparison group, students who complete the CAST elective will report being significantly more prepared to identify signs of maltreatment;
2. Relative to students in the comparison group, students who complete the CAST elective will report being significantly more prepared to report a case of suspected maltreatment;
3. Relative to students in the comparison group, students who complete the CAST elective will report being significantly more likely to report suspected maltreatment, even if they did not know for sure it happened;
4. Relative to students in the comparison group, students who complete the CAST elective will report being significantly more prepared to recommend or secure needed services for a maltreated child or adolescent; and
5. Relative to students in the comparison group, students who complete the CAST elective will demonstrate improved knowledge in the areas of maltreatment identification and reporting.

8.2 Our project

Eighty-nine of a total class of 177 first year medical students at a large Mid-western college of medicine stated their intentions to participate and were enrolled in the study. Of these, forty chose to enroll in the elective course, and all of these students completed both pre- and post-test measures. This group (“CAST elective group”) included nine males and 31 females. Of these, 30 students identified as “Caucasian or White,” seven as “Asian” and three as “Other.” Thirty-two students in the CAST elective group reported having received 0–1 hour of training in the area of maltreatment prior to study participation. Six in the CAST elective group reported having received 2–4 hours. Two students in the CAST elective group reported 8+ hours of prior training in the area of maltreatment.

The comparison group consisted of 49 students who did not sign up for the elective but agreed to participate in the study. This group consisted of 31 males and 18 females. Fourteen students in the comparison group failed to complete the post-test measure for unknown reasons. Thirty-three students in the comparison group identified as “Caucasian or White,” three as “Black/African American,” nine as “Asian,” one as “Hispanic/Latino” and three as “Other.” Thirty-five students in the comparison group reported having received a total of 0–1 hour of training in the area of maltreatment prior to study participation. Twelve students in the comparison group reported having received 2–4 hours. One student in the comparison group reported 5–7 hours of training prior to participation. One student in the comparison group reported 8+ hours of prior training in the area of maltreatment.

A total of 75 students fully completed the study. The mean age for the entire sample was 22.82 years ($SD = 1.74$). Participants ranged in age from 19 to 29 years old. Of the study completers, 52 students identified as "Caucasian or White," 2 as "Black/African American," 14 as "Asian," one as "Hispanic/Latino" and 6 as "Other."

8.2.1 Measures

Demographic information on all participants was collected before all other questions on the pre-test measure were asked. Participants reported their age, gender, ethnicity, and total number of hours of prior training in maltreatment. At both pre- and post-test, medical students' perceived preparedness to identify and report maltreatment were both assessed using a 5-point Likert scale ranging from "Very Unprepared" to "Very Prepared," with a neutral mid-point. Additionally, participants were asked how prepared they feel to recommend or secure needed services for a victim of maltreatment using a 5-point Likert scale ranging from "Very Unprepared" to "Very Prepared." Participants also were asked to determine how likely they would be to report suspected maltreatment even though they did not know for sure that it was occurring using a 5-point Likert scale ranging from "Very Unlikely" to "Very Likely," with a neutral mid-point.

Students' actual ability to identify and report maltreatment was measured at both pre- and post-test using analog vignettes. Vignettes were written to depict situations likely to occur in medical practice settings. Although the larger study included vignettes depicting maltreatment in a variety of different developmental stages, to be consistent with the focus of this issue, only those pertaining to adolescence (four) were included in this analysis. To most effectively evaluate true mastery of the concepts taught, the vignettes illustrated challenging or difficult aspects of adolescent maltreatment cases (e.g., threatened harm without evidence of actual prior abuse; individuals with physical and/or developmental disabilities who are older than 18 years of age; see Appendices A–D). Some vignettes were developed to evaluate participants' ability to identify levels of suspicion and possible harm that may require reporting in cases that lack objective, definitive data indicating maltreatment. This dilemma parallels reality in that physicians often do not report suspected or questionable maltreatment because they believe they do not have enough information to be sure (10). The vignettes used were written according to the state laws on reporting abuse and neglect for the state in which the medical school was located. The vignettes used in this study were independently validated by a Board Certified Child and Adolescent Psychiatrist, a Licensed Clinical Psychologist, a Licensed Professional Clinical Counselor-Supervisor and an Attorney specializing in child and adolescent advocacy. There was 100% agreement in correct responses, across all raters, for all vignettes reported in this study. In accordance with

the expert responses, “Yes” responses were considered correct for each of the eight vignette questions. Total scores were obtained by adding together the total number of correct responses on the scale.

8.2.2 Procedures

All first-year medical students at the medical school were contacted by email and invited to participate in a credit/no-credit elective course. Students were told that they would learn about child and adolescent advocacy, maltreatment and its consequences, and professional responses to maltreatment. The elective was one of 17 pre-clinical elective courses offered to the students. The elective courses are optional for medical students, and offered to provide more in-depth training in areas of interest than is typically covered in the main curriculum. All preclinical electives are graded on a Credit/No Credit basis. Full participation in preclinical electives results in the receipt of “credit” for the elective on the student’s transcript. Failure to meet participation requirements for an elective in which a student has enrolled results in the receipt of “no credit” recorded on the transcript.

Students enrolled in the elective course were asked to participate in a study examining the effectiveness and utility of the course material. They were informed that participation in the study would require their time and effort to complete a battery of self-report questions and questions about short vignettes prior to completion of the elective course and again after completing the course.

Students in the CAST elective group received an orientation at the beginning of the elective and attended didactic presentations to learn and discuss a variety of topics concerning maltreatment and advocacy. Students also met with faculty for informal, small group mentoring sessions. The students’ involvement included a total of 20 hours of didactics and case discussion, approximately 2–4 hours of time with patients on the inpatient unit, independent study and preparation of papers/presentations as follows:

1. Two-hour meeting every other month, during which faculty and related professionals presented relevant topics, presented videos and documentaries, and facilitated discussion. Topics included: definition of child and adolescent maltreatment, prevalence, risk and protective factors, role of professionals in addressing maltreatment, reporting suspected maltreatment, physical and mental health indicators of maltreatment, medical perspectives on maltreatment, cycles of family violence, promoting social change, corporal punishment and physical abuse, physician anticipatory guidance for prevention of maltreatment, child and adolescent sexual abuse prevention, advocacy for maltreated children and adolescents, characteristics of sexual offenders and sexual offenses, domestic violence and health care, screening for maltreatment

- and domestic violence, and resources for families affected by maltreatment. Professionals leading these lectures and discussions were from the following professions: psychiatry, psychology, pediatrics, social work, and advocacy/law
2. 1–2 hours in smaller group (15–20 students per smaller group) case discussion with faculty in child and adolescent psychiatry, pediatrics and related professionals on alternating months
 3. Observation of one patient on the child and adolescent psychiatric inpatient unit with focus on the impact of adverse events on children and youths. Students interacted with their assigned patients using games and casual discussion only (not clinical interviews, etc.). They read the patients' charts and discussed the cases with inpatient staff members. Students were required to initiate discussion about the cases at the smaller-group discussion meetings. There were no time requirements for students' case discussions. Cases were discussed for approximately 5–30 minutes, depending on the number and type of questions raised by the other students and the case
 4. Each student studied one de-identified case involving suspected maltreatment. These were outpatient cases that had been evaluated and treated at the child and adolescent psychiatric mental health facility at the medical college hospital. Students were required to develop and submit a (3 page) paper or 20 minute presentation about the case. Thirty-six students wrote a paper, and four students made presentations about their assigned cases

A comparison group of first-year medical students was included in the study design in order to thoroughly examine the efficacy of the elective course compared to the usual medical curriculum. Students in the comparison group were recruited via the clubs and groups in the medical school and were asked participate in a study examining the effectiveness and utility of course material on maltreatment. Comparison group participants were also informed that study participation would require their time and effort in completing a battery of self-report questions and questions about short vignettes during the fall semester of the 2011–2012 academic year and again at the end of spring semester of the 2011–2012 academic year. Participants in the comparison group completed the same battery of self-report questions and vignettes as the elective group at the same data collection time points.

The Institutional Review Board designated the study “exempt” and did not require written consent for participation. Students were told verbally that their answers are anonymous, they should not write any personally identifying information on the questionnaires, and that they had the right to refuse to take part or withdraw at any time without consequences. The pre- and post-test questionnaires were administered by study personnel (not faculty or other educators) in the classroom immediately prior and immediately following students' completion of the elective.

8.2.3 What we found

Chi square and t-tests analyses were used to compare the CAST elective and comparison groups on the following demographic variables: sex, age, ethnicity, and number of hours of prior training in maltreatment. The groups differed only on the sex variable chi squared (χ^2) (1, $N = 75$) = 14.79, $p < 0.0001$, indicating that there were more males in the comparison group. In addition, to determine if there were any identifiable patterns of attrition, the 14 students who dropped out of the study were compared to the rest of the sample on the same demographic variables. These groups did not differ on sex, age, ethnicity or number of hours of prior training in maltreatment. Due to the imbalanced proportion of males to females between groups, all subsequent analyses conducted controlled for sex.

Repeated measure ANOVAs (with the variable “sex” as a covariate) were conducted to compare the responses of students in the elective and comparison groups over time. There was a statistically significant time by group interaction for perceived preparedness to identify signs of maltreatment, $F(1,72) = 29.87$, $p < 0.0001$, $\eta^2 = 0.29$. This effect favored the CAST elective group, suggesting this group’s scores on this item increased significantly more than did the comparison group’s scores from pre-test to post-test. There was also a significant time by group interaction favoring the CAST elective group for students’ perceived preparedness to report a case of suspected maltreatment, $F(1,72) = 47.62$, $p < 0.0001$, $\eta^2 = 0.40$. There was a statistically significant time by group interaction favoring the CAST elective group for perceived likelihood of reporting maltreatment if they suspected, but did not know for sure, that maltreatment occurred, $F(1,72) = 17.10$, $p < 0.0001$, $\eta^2 = 0.20$. Lastly, there was a significant time by group effect on students’ perceived preparedness to recommend and/or secure services for a maltreated child, $F(1,72) = 27.91$, $p < 0.0001$, $\eta^2 = 0.28$.

Table 8.1 depicts percentages of the CAST elective and comparison groups with correct responses to each of the eight vignette questions. To examine changes in student knowledge about maltreatment, CAST elective and comparison group vignette total scores were compared across time using repeated measures ANOVA (with the variable “sex” as a covariate). There was a statistically significant time by group interaction on vignette total scores favoring the CAST elective group, $F(1,72) = 4.77$, $p = 0.032$, $\eta^2 = 0.06$.

8.3 Conclusions

The purpose of the current study was to examine the effects of training medical students using a CAST elective course. It was expected that medical students’ self-reported preparedness to address maltreatment and likelihood of reporting suspected maltreatment would increase significantly following CAST training, relative to a comparison group. In addition, it was anticipated that students’ knowledge in the areas

Table 8.1: Percent correct on vignette questions at pre and post by group
(N = 75, CAST elective: n = 40, comparison: n = 35)

Vignette	Elective group (%)	Comparison group (%)
Pre-test vignette #1: Abuse	52.2	38.8
Post-test vignette #1: Abuse	87.5	40.0
Pre-test vignette #1: Report	40.0	30.6
Post-test vignette #1: Report	77.5	34.3
Pre-test vignette #2: Abuse	97.5	98.0
Post-test vignette #2: Abuse	100.0	97.1
Pre-test vignette #2: Report	90.0	91.8
Post-test vignette #2: Report	100.0	91.4
Pre-test vignette #3: Abuse	90.0	87.8
Post-test vignette #3: Abuse	97.5	88.6
Pre-test vignette #3: Report	77.5	71.4
Post-test vignette #3: Report	92.5	68.6
Pre-test vignette #4: Abuse	77.5	89.8
Post-test vignette #4: Abuse	95.0	91.4
Pre-test vignette #4: Report	85.0	87.8
Post-test vignette #4: Report	92.5	91.4

CAST: child advocacy studies training.

Abuse: "Is this child being maltreated? ", Report: "Would you report this case to Children's Services?", All responses were "yes" or "no."

of maltreatment identification and reporting would improve relative to comparisons. Results supported all five of the study's hypotheses. Results indicate that students in the CAST elective reported higher degrees of preparedness to report and likelihood of reporting suspected maltreatment. Results also suggest that students in the elective group did, in fact, demonstrate improved knowledge in identification and reporting of adolescent maltreatment compared to students in the comparison group who did not receive training in the areas of advocacy and maltreatment. Students in the elective group not only did better at identifying the maltreatment depicted in the vignettes, but they also demonstrated improved ability to determine which cases should be reported. Thus, these results indicate that both perceptions and actual knowledge were improved for students who completed the CAST elective. The fact that elective students' knowledge and preparedness improved relative to a comparison group indicated that the students' scores on the measures did not increase due to some factor (e.g., other medical didactics, life experience) other than the CAST training. Results suggest that general training in child and adolescent maltreatment and advocacy in the first year of medical school has the potential to improve future physicians' knowledge and likelihood of effectively identifying and reporting suspected maltreatment.

Although as expected, the percentage of correct responses to vignette questions did increase for the elective group, relative to comparisons, it is important to note there was not 100% correct responding in the elective group. This finding suggests

that there is room for improvement in teaching the identification and reporting of adolescent maltreatment. For example, the first vignette depicted an 18-year-old with severe mental retardation who often stays home alone for long periods of time. The majority of the total sample responded incorrectly to questions about this vignette at pre-test. Although most elective students' scores improved following the elective, twelve percent still got this answer wrong at post-test. This may suggest a need for more thorough training or case examples about reporting maltreatment of individuals with disabilities, indicators of neglect, and/or age limits stipulated in state reporting laws.

Furthermore, it is important to note that reporting rates should have been consistent with rates of identifying maltreatment. That is, if a case was endorsed as an example of suspected maltreatment, it should also have been endorsed as worthy of reporting, and therefore rates of identifying and reporting should have been identical. However, there was not 1:1 correspondence in that some cases judged to be maltreatment were not judged to be reportable. This pattern of findings suggests a need to improve teaching about mandatory reporting of all cases of suspected abuse.

Results of the current study should be considered in light of certain limitations. Although the use of a comparison group was a strength of the study, there was not random selection from the medical student population nor was there random assignment to groups. Random assignment would have improved the likelihood of true group equivalency and improved the generalizability of the findings. The groups in the present study were not equivalent with respect to participant sex, with the comparison group having a higher proportion of males. Because males have been shown in some studies to be less likely to report maltreatment (11), this may have affected the findings. Further, the lack of random selection increases the likelihood that the students who chose to take the CAST course are not representative of medical students in general. Lastly, there was disproportionate drop-out in that all of the non-completers were from the comparison group. If possible, to prevent these issues, future studies should make use of random selection and random assignment to groups.

The fact that the sample was restricted to only one school limits the implications that can be made from the study. Future studies should replicate these findings at multiple sites in a variety of geographical regions, from schools with diverse student populations. Subsequent studies on the CAST program also should evaluate whether the effects last beyond medical training, and improve physician practice in maltreatment and advocacy.

If replicated, these results would suggest that the CAST program may be an effective method of better preparing future physicians to address child and adolescent maltreatment. Broad dissemination of the program in medical schools across US could, in turn, have a significant positive impact on reducing child and adolescent maltreatment on a national level. This would represent a major advance in protecting children and adolescents and reducing human suffering.

8.4 Appendices

8.4.1 Appendix A

An 18-year-old female with developmental disabilities (severe mental retardation) attends her annual physical exam. During the appointment, the girl's mother talks about how stressed she has been as she struggles to work three jobs in order to make ends meet while trying to tend to the constant special needs of her teenager. She also mentions that finding someone to stay with the girl while she goes to work has been problematic. Mother mentions that the girl often stays home alone while she is at work.

- | | | |
|---|-----|----|
| 1. Is this child being maltreated? (Please circle one.) | Yes | No |
| 2. Would you report this case to Children's Services?
(Please circle one.) | Yes | No |

8.4.2 Appendix B

A 15-year-old girl comes in for a physical to get medical clearance to play soccer for her high school. During the visit, the teenager asks the physician for advice about a situation that happened at her friend's house the last two weekends. She explains that her friend's stepfather has been watching pornography and does not allow the girls to leave the room. The teenager says that she feels uncomfortable because her friend's stepfather touches his private parts while watching the pornography.

- | | | |
|---|-----|----|
| 1. Is this child being maltreated? (Please circle one.) | Yes | No |
| 2. Would you report this case to Children's Services?
(Please circle one.) | Yes | No |

8.4.3 Appendix C

A 20-year-old male with transverse myelitis is seen for a regular check-up. The young man relies on a wheelchair for mobility and has to depend on his father's girlfriend when he wishes to leave the home. His father reports that his son recently admitted to showing his penis to his father's girlfriend on several occasions. Per father's report, the young man told his father he did not want to show his penis, but he only does it because father's girlfriend refuses to take him to the store if he does not follow her sexual requests.

- | | | |
|---|-----|----|
| 1. Is this child being maltreated? (Please circle one.) | Yes | No |
| 2. Would you report this case to Children's Services?
(Please circle one.) | Yes | No |

8.4.4 Appendix D

The mother of a 12-year-old girl and 10-year-old boy reports that her ex-husband has been threatening to lock her children in the dark basement for the weekend with no food if they continue to refuse to eat dinner while at his house every other weekend. While mother is explaining her concerns, the girl interjects and says, “He really will do it, too – he did it to Kris before!” Mother reports that Kris is her children’s half sibling.

- | | | |
|---|-----|----|
| 1. Is this child being maltreated? (Please circle one.) | Yes | No |
| 2. Would you report this case to Children’s Services?
(Please circle one.) | Yes | No |

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9 Bullying, psychiatric pathology and suicidal behavior

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Bullying is a highly prevalent behavior which carries a significant social, medical and financial cost for its victims and perpetrators, with powerful and long lasting psychological and social impact. Bullying has been defined as a specific form of intentional, repeated aggression, that involves a disparity of power between the victim(s) and perpetrators(s). The aggression can take physical, verbal, or gestural forms. The behavior of bullying crosses sociodemographic categories of age, gender, ethnicity, level of academic achievement and professional environment. It has been abundantly observed by teachers and parents in elementary schools, but has also shown its negative presence in corporate boardrooms. The direst outcome of bullying, for both victims and perpetrators, is an increased risk of psychiatric disorders including depression, post-traumatic stress disorder, anxiety disorders, substance abuse, and suicidal behavior. Cruelty (and bullying, as one of its manifestations) break the basis of morality. Mental health professionals usually treat the victims of those actions unfortunately long after they have been exposed to the harm. The evidence does not support the idea that the majority of cruel actions are intrinsically “pathological,” in the sense of being motivated by “mental disorders.” Therefore, only moral rules and legal actions – but not psychiatric or psychological interventions – may dissuade humans from this form of cruelty.

9.1 Introduction

The behavior of bullying carries a direct, significant social, medical and financial cost for its victims and perpetrators. Bullying can also cause an indirect harm to our social progress, a cost that is much harder to measure. Data demonstrates that bullying is a highly prevalent behavior, with powerful and long lasting psychological and social impact on its victims and perpetrators (1). Interestingly, the behavior of bullying crosses sociodemographic categories of age, gender, ethnicity, level of academic achievement and professional environment. It has been abundantly observed by teachers and parents in elementary schools, but has also shown its negative presence in corporate boardrooms (2–4).

Any involvement in bullying can impair the quality of life in victims, as well as for perpetrators of this reprehensible behavior. For example, Connolly and colleagues (5) have demonstrated that children who bully are at higher risk of developing severe relationship problems as adults. The trauma of bullying has been shown to be associated with severe and chronic psychiatric pathology, including mood and anxiety disorders, PTSD, alcohol and drug abuse as well as personality disorders (6). The most alarming sequela of bullying, however, is its significant association with

suicidal behavior (7). Thus, given the high social, personal and medical cost of bullying, these social behavioral phenomena should be conceptualized as a source of severe trauma that can lead to psychiatric conditions. Thus, it should be approached from a multidisciplinary perspective involving teachers, parents, and mental health professionals (7).

9.2 Definition

There is a lack of consensus on exactly what comprises “bullying,” and academic arguments continue reshaping the surface of its definition. A general framework of bullying, however, has been established and accepted by the community of researchers involved in this subject matter. Olweus (8) defined bullying as a specific form of intentional, repeated aggression, that involves a disparity of power between the victim(s) and perpetrators(s). The aggression can take physical, verbal, or gestural forms. It can also be enacted through intentional exclusion of a person from a group, without apparent provocation on the part of the person being excluded. What sets bullying apart from other forms of abuse or violence is the social context in which it occurs and the imbalanced power relationship of the parties involved (8).

9.3 Demographics of bullying behavior

Wang and colleagues (9) have recently shown that, among US adolescents, the prevalence of having bullied others or having been bullied at school for at least once in the last 2 months were 20.8% physically, 53.6% verbally, 51.4% socially, and 13.6% electronically. Males were more involved in physical and verbal bullying, whereas girls were more involved in relational bullying. Boys were more likely to be cyber bullies, whereas girls were more likely to be cyber bullying victims. Compared with 6th graders, 9th and 10th graders were less involved in bullying for physical (as bullies, victims, or bully-victims), verbal (as victims or bully-victims), relational (as victims or bully-victims), and cyber (bullies) form.

African-American adolescents were involved in more physical, verbal, or cyber bullying, but were found less likely to be victims of bullying. Higher parental support was associated with less involvement across all forms of bullying, and having more friends was associated with more bullying and less victimization for physical, verbal, and relational forms. However, this did not have a protective effect for cyber bullying. Lemstra et al (10) investigated bullying in 4,197 youth subjects in which 23% reported being physically bullied at least once or twice in the previous four weeks. They demonstrated that being male, attending a school in a low-income neighborhood, perception of having unhappy home life, arguments with parents and the desire to leave home have been found to be factors that may leave youth vulnerable to bullying.

It is also important to recognize that bullying occurs outside of middle and high school settings. Murhtar and colleagues (2) found that almost 70% of medical students had experienced some form of bullying in the past 6 months. Balducci et al (3) demonstrated that bullying is a prevalent behavior in the workplace, and a study of the Norwegian workforce by Nielsen and colleagues (4) demonstrated that, even in egalitarian Norway, almost 5% of people see themselves as victims of bullying, with nearly 7% reporting that they are exposed to a high degree of bullying behaviors and 1% reporting that they are exposed to severe bullying.

9.4 Bullying and suicidal behavior

As previously mentioned, the direst outcome of bullying, for both victims and perpetrators, is an increased risk of suicidal ideation, suicidal attempts and completed suicide. A study that involved 838 9th–12th graders attending public high school demonstrated that subjects involved in bullying as a perpetrator, victim, or victim-perpetrator were more likely than controls to report having seriously considered or attempted suicide within the past year (11). Fisher and colleagues (12) demonstrated in twin studies that exposure to frequent bullying predicted higher rates of self-injurious behavior, even after controlling for pre-morbid emotional or behavioral problems and environmental risk factors. A study by Winsper et al (13) showed that pre-adolescence subjects involved in bullying, especially in the role of being both a bully and a victim, were at increased risk for suicidal ideation, suicidal attempts and self-injurious behavior. Brunstein and colleagues (14), however, suggested that bullying behavior in the absence of depression or suicidality is not an independent risk factor, but rather amplifies inherent risk of suicidal behavior associated with depression.

9.5 Bullying and psychiatric pathology

Regardless of whether bullying increases the risk of suicidal behavior independently of psychiatric pathology, it is important to understand that bullying is, in fact, associated with a number of psychiatric conditions, all with inherent risk for suicidal behavior. Kumpulainen et al (6) have shown that young subjects involved in bullying are more likely to struggle with disorders such as attention-deficit hyperactivity disorder, depression, anxiety, and personality disorders.

9.6 Bullying and depression

Multiple studies have demonstrated a clear correlation between involvement in bullying and a higher risk of developing a depressive disorder. Lemstra and colleagues (15)

showed that children who were physically bullied multiple times per week were 80% more likely to develop symptoms of depression in comparison to controls who never experienced bullying. A retrospective study by Lund et al (15) claimed that adult men with a self-reported history of being bullied at school were significantly more likely to be diagnosed with a depressive disorder later in life. A prospective study that looked at 2,348 young boys (16) demonstrated that subjects who were both perpetrators and victims of bullying were at higher risk for developing depression and suicidal behavior later in life.

9.7 Bullying and PTSD

Bullying, although not considered to be a form of acute trauma, has been shown to be associated with symptoms of Post-Traumatic Stress Disorder (PTSD). Positive correlation between symptoms of PTSD and exposure to bullying were also demonstrated among subjects who experienced bullying at work (17). Another study that attempted to assess prevalence and intensity of PTSD symptomatology among victims of bullying at work demonstrated that more than 70% of bully victims developed symptoms of PTSD and displayed a moderate or severe impairment in social functioning (18).

9.8 Bullying and anxiety disorders

People involved in bullying also appear to be at a higher risk of anxiety disorders other than PTSD. One study demonstrated that social phobia, obsessive compulsive disorder and panic disorder were all positively associated with severe teasing and bullying experiences (19). Kumpulainen et al (20) showed that, among children victims of bullying, anxiety symptoms were as frequent as 8.7%, significantly higher than controls. Another study demonstrated that being a bully, victim of bullying, or having a role of being both a bully and victim in preadolescence (aged 10–12 years) (21) significantly predicted development of anxiety symptoms in adolescence (aged 10–17 years) (22). Data also supports a strong, positive correlation between involvement in bullying and development in anxiety symptoms in younger children, those in grades 5 through 8, and students aged 12–17 years (23).

9.9 Bullying and substance and alcohol abuse and dependence

Finally, research has consistently demonstrated that subjects involved in bullying are more likely to use alcohol and illicit psychoactive substances. In one large sample, it was shown that substance use and bullying behaviors co-occurred among 5.4% of adolescents in the US (24). A nationally representative survey of 6th–10th graders in

the US found that alcohol use was associated with increased odds of bullying (25). A study of adolescents ages 12–17 years who were admitted to inpatient psychiatry units showed that the use of any substance (e.g. tobacco, alcohol and drugs) was generally more common among bullies (26). Finally, a large study based on school children demonstrated that students who were engaged in bullying were more likely to be smokers and to have had a history of alcohol use (27).

9.10 Philosophical considerations

“Bullying” is a term that describes the nature of some “cruel” action (taking place primarily, but not exclusively, in the school environment), as the term “child sexual abuse” perpetrated by relatives is the new, scientific word currently used when referring to “incest”. Cruelty, though not always violent, is always aggressive. Moreover, it is a phenomenon linked to human nature. It happens when one inflicts pain on the other with apparent provocation (as opposed to “revenge” or even “justice”). Most importantly, cruelty happens in asymmetric relationships: a “master” (who possess and exerts the power) uses physical and/or verbal violence against a “slave” (the victim) who is always in a weaker position and has no or insubstantial defense (28). Sometimes the “master” is not represented by a single individual but by a group, and the nature of this relationship is not stable and may change in the future. Victims may be cruel to other victims, or they may engage in cruel behavior to a former master if a former master “falls” in the social order.

In any case, the gratuitous nature of cruel actions and their independence from sexual gratification make them different from “sodomasochism.” It also differs from revenge as it has not been motivated by any previous harm. From an evolutionary perspective, we could add that it has no relationship with self-defense and/or with the “struggle for life.” The German philosopher Schopenhauer (1788–1860) said that the unbearable suffering of living leads to those expressions of violence, following the fantasy of being able to “master” that life anguish through the exercise of power against another human being (29).

From the philosophical point of view, we can either follow the Hobbesian view, according to which cruelty is an innate characteristic of all human beings (“*homo homini lupus*”) (30), or we can share Rousseau’s thesis (mankind is a good and innocent specie that has been spoiled by society) (31). Some philosophers underline the role of the individual, others, the role of the nature of the relation (i.e., the “systemic” approach).

Nevertheless, cruelty (and bullying, as one of its manifestations) break the basis of morality. We, as mental health professionals, usually treat the victims of those actions unfortunately long after they have been exposed to the harm. Perpetrators of bullying generally (but not always) must bear with the sanctions society has developed to control violence, and they are often reluctant to participate in psychological interventions. In any case, the evidence does not support the idea that the majority

of cruel actions are intrinsically “pathological,” in the sense of being motivated by “mental disorders,” but a human phenomenon related to the nature of our condition. Therefore, only moral rules (expressed, for instance, in educational models) and legal dispositions – but not psychiatric or psychological interventions – may dissuade humans from this form of cruelty.

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10 Dating violence and suicidal behavior in adolescents

Kristin Holmes and Leo Sher

The aim of this chapter is to assess the possible consequences of adolescent physical, emotional and sexual dating violence through a review of the literature on the topic. An electronic search of major biomedical bibliographic databases (Pubmed, ISI, Psyc INFO) was used to retrieve articles providing information on the prevalence rates, risk factors, associated consequences and possible preventive measures for adolescent dating violence across different populations. Currently, there have been few longitudinal studies conducted to identify potential risk factors for entering a violent dating relationship in adolescents. Risky behaviors such as earlier sexual intercourse may predispose someone for victimization. Dating violence itself is also a predictor of future dating violence. Adolescent dating violence was associated with an increase in other violence-related behaviors, substance use, depression, poorer educational outcomes, post-traumatic stress, unhealthy weight control, and risky sexual behavior. The association between adolescent dating violence and an increase in suicidal behavior is a major public health concern. Future research should focus on longitudinal studies so that a causal relationship between dating violence and suicidality may be better understood.

10.1 Introduction

Approximately 9% of adolescents are victims of dating violence (1). As this review of the current literature reveals, dating violence has numerous physical and psychological implications, the most serious of which is suicidality. The prevalence of dating violence in adolescent relationships and its consequences (including suicidality) is discussed and purported risk factors for its occurrence are reviewed. Additionally, limitations of the current research are examined and directions for future research and prevention are proposed.

According to the Center for Disease Control and Prevention (CDC), adolescent partner violence can be characterized along four dimensions: emotional, physical, sexual, and stalking (1). Each categorization consists of a number of violent behaviors, which range in severity. Emotional dating violence includes verbal abuse, and jealous or controlling behaviors such as preventing the partner from talking to members of the opposite sex, checking text messages or emails, or not allowing the partner to keep in touch with members of his or her friends and family. Physical dating violence consists of everything from pushing or restraining to hitting, punching, choking, or the use of a weapon against one's partner. Sexual dating violence includes uncomfortable remarks as well as any unwanted sexual experiences. Stalking includes threats or patterns of harassment that are used to instill fear in the victim (1).

10.1.1 Literature search

An electronic search of the major biomedical bibliographic databases (Pubmed, ISI, PsycINFO) was conducted to retrieve articles published between the years 2000 and 2012 describing the social, epidemiological and clinical characteristics of dating violence and its relationship to suicidal behavior in adolescents. Key words for the search included “adolescent,” “teen,” “dating violence,” “victimization,” “abuse,” “suicide,” and “suicidal behavior.”

10.2 Findings

Upon analysis of the prevalence of dating violence in adolescents, it becomes apparent that this is a widespread problem among youth. Across both genders, approximately 9–17% of adolescents report physical dating violence (2, 3). The variation in prevalence rates may be attributable to differences in sample populations. Among New York City youth, 10.6% of females and 9.5% of males reported physical dating violence (4). Similar results were found in a nationally representative sample of boys with 9.13% reporting physical dating violence (5).

A study focusing on Black and Hispanic youth found that approximately 10% of youths reported dating violence victimization in the past year (6). In a survey study of Latino youths aged 11–13 residing in suburban Washington DC, prevalence of dating violence was 14.4% for girls and 12.9% for boys (13.5% across the sample) (7). Prevalence of dating violence among adolescent boys was highest for those who classified themselves as black or ethnically “other” (5). These slightly higher rates of dating violence among minorities may be due to socio-economic status or cultural differences.

In a study of New York City youth, 9.6% of females and 5.4% of males reported a lifetime history of sexual assault (4). 13.2% of adolescents in a large survey of students in grades 7–12 reported unwanted sexual experiences perpetrated by a peer (2). A study focusing on Black and Hispanic youth found that approximately one in 10 youths reported dating violence victimization in the past year and 1 in 10 girls reported a history of sexual assault in her lifetime (6). Analysis of the 1997 and 1999 Massachusetts Youth Risk Behavior Surveys revealed that about one in five female adolescents had been a victim of physical and/or sexual dating violence (20.2% in 1997 and 18.0% in 1999) (8). Another large survey-based study found that 24.6% of youths in grades 7–12 reported at least one of these forms of victimization (2).

Although both boys and girls experience dating violence victimization, in a study of 190 high school students, girls reported higher levels of severity and frequency of dating violence (9). In concurrence, another study found that males are more apt to engage in severe forms of physical aggression (4.6% vs. 2.0%) that result in serious medical consequences for the victim (10). Females, however, reported a significantly higher percentage of verbal aggression than males (10).

10.2.1 Risk factors

To date, most research on adolescent dating violence has been cross-sectional in nature. Thus, while many risk factors for engaging in adolescent dating violence have been proposed (i.e., exposure to domestic violence in the family of origin, low socioeconomic status, etc.), they have yet to be validated scientifically. Similarly, a causal relationship between mental health symptoms such as depression, anxiety, or suicidality and dating violence cannot be established. There have been a few longitudinal studies, however, that provide some insight into precursors for and consequences of adolescent dating violence.

One such study proposed several potential risk factors for dating violence (11). This study followed girls dating in grade 9 in an attempt to predict profiles of dating relationships in grade 11 based on the girls' relationships with families and peers. They found that an adolescent girl's involvement in a mutually violent dating relationship in grade 11 could be facilitated by several risk factors (i.e., delinquency, parental rejection, and sexual harassment perpetration) evident during grade 9. Moreover, girls in grade 11 who reported being solely victims in violent dating relationships had higher rates of sexual intercourse in grade 9 (11). This implies that early relationships may predispose a girl to future victimization during later adolescence. Sexual relationships at this young of an age may directly place girls at more risk for later physical violence. Or, perhaps these girls have some personality characteristics that lead them to relationships with a certain aggressive type of male or to engage in riskier behaviors that consequently make them more vulnerable to victimization.

Dating violence in itself is a risk factor for further dating violence. One study found that 8% of boys and 15% of girls were persistently aggressive with the same partner over a period of 3 months. In a year-long longitudinal study of dating aggression in Canadian high-school students, 13% of participants reported recurrent dating aggression across two different relationships (12). Of the remaining participants, 55% reported no dating aggression at either point and 32% reported dating aggression in one of their relationships during this time period. This study was unique as it was the first to study recurrent aggression across multiple dating relationships. Different patterns of aggression emerged from these groups. For those who reported dating violence in only one relationship, frequency of dating aggression was low (most reporting that the acts occurred "rarely") and the severity was reported as being minor (pushing, grabbing, or shoving). For those who reported aggression in two relationships, the frequency of aggression was higher at the second data collection point. Also, most adolescents reported that aggression occurred in both directions, with each partner acting as a victim and a perpetrator (12). Another study also found that victimization in a dating relationship predicted perpetration (13). Therefore, being a victim of dating violence not only puts an adolescent at risk for further victimization, but also becomes a risk factor for perpetration.

These findings suggest that patterns emerge in early relationships that make an adolescent vulnerable to victimization and/or perpetration of physical dating violence. If these risk factors are identified early on, later dating violence could be prevented. Perpetration of physical violence can be predicted by previous victimization and engagement in psychological aggression (i.e., verbal aggression, jealous behavior, and controlling behavior) (14). Due to this “circle-of-violence” in which the victim evolves into the perpetrator, it is especially important to intervene at early stages and break this cycle before violent patterns are materialized.

10.2.2 Psychiatric and social consequences of dating violence

Cross-sectional studies found that dating violence was associated with an increase in other risk behaviors and mental health consequences such as violence-related behaviors, substance use, depression and suicidal ideation (3). Dating violence was also associated with poorer educational outcomes (2), post-traumatic stress (9), and unhealthy weight control including diet pill use, laxative use and vomiting (8). In a nationally representative sample, risky sexual behavior was also associated with physical dating violence (5, 8). More specifically, those boys who reported two or more sexual partners in the past 3 months, compared with those who reported none, were over three times more likely to report violence (5).

Two different US surveys of risk behavior in youths found an association between drinking alcohol, smoking cigarettes and using cocaine with dating violence (5, 8). In a study of Latino early adolescents, girls who binge drank were 27 times more likely to report dating violence (7). The association between current alcohol consumption and dating violence was also seen among male high-school students in central Thailand further proving that this finding extends to many different cultures (15).

10.2.3 Dating violence and suicidality

Suicidality is a serious consequence of adolescent dating violence. The adolescent suicide attempt rate is high, with a 2005 New York City survey finding that 11.7% of female and 7.2% of male adolescents have made one or more suicide attempts (4). Dating violence victimization may be a significant risk factor for adolescent suicidality as they were found to be associated in several studies (6, 16). In one study of adolescent abortion patients, dating violence was related to severity of suicidal thinking; and, as the severity of the adolescent females’ general problems with aggressive behavior rose, the magnitude of the relationship between dating violence and severity of suicidal thinking increased (17). This suggests that there may be personality traits or psychiatric illnesses that mediate the relationship between dating violence and suicidality. In another study, female Asian-American and Pacific Islander youth

were significantly more likely to consider suicide and to have made a suicide attempt than males (18). Therefore, dating violence victimization may be a greater hazard for female adolescents than male. Even though dating violence can increase the frequency and severity of suicidal thoughts and increase the risk of making an attempt, research on this topic is sparse. Additional research with a broader sample would be beneficial to the development of prevention initiatives for both adolescent dating violence and suicidality.

10.3 Discussion

There are many theoretical mechanisms which may account for an increase in suicidality resulting from dating violence. While dating violence can directly increase the risk for suicidality in the victim, it more often leads to other health consequences, which in turn bolster suicidal ideation and behavior. These consequences act as mediators, as they facilitate the risk for suicidality, due indirectly to engagement in dating violence.

One such mediator could be the multitude of negative mental health consequences that were discussed earlier such as depression, anxiety, post-traumatic stress, substance use, or disordered eating patterns. These mental health outcomes in turn increase the risk for suicidal thoughts or behaviors in the victim. Another possible mediator, which requires further study, is the medical consequences associated with dating violence. Some medical consequences of dating violence such as bruises, broken bones, and cuts have been discussed. As these adolescents grow older, the medical consequences may become even more severe leading to injuries requiring major medical stabilization or a lifetime of disability such as traumatic brain injuries (TBIs). It is very likely that these medical consequences can lead to an increase in suicidal behavior. For example, multiple lines of evidence suggest that TBIs are associated with suicide attempts and suicides (19, 20).

There may also be more complicated mechanisms facilitating suicidality in this population. Psychiatric illnesses such as depression or substance use may predispose an adolescent to violent dating relationships. Therefore, the adolescent is more likely to have an increase in suicidality after involvement in dating violence because of the pre-existing mental health issue. Suicidal behavior may have a possible genetic component that may be mediated by familial transmission of impulsive aggression (21).

Finding a method to reduce suicidality in adolescents is of extreme importance. Dating violence is one reason an adolescent may suffer from suicidal thoughts and have made one or more suicide attempts. Identifying at-risk youth should be the first step towards prevention of both dating violence and suicidality. Early detection of risk factors for suicidal behavior may help identify families that are at risk (21). This is important because the family unit is an integral part of the adolescents' development and family connectedness is inversely related to dating violence (3). If an at-risk

family is identified early-on, perhaps the family can receive the resources they need to promote family connectedness and prevent negative developmental outcomes such as depression, substance abuse, dating violence and suicidality.

Educating those families and youth that are at risk about dating violence should be the next step after identification towards prevention. Media may be a beneficial means to educating adolescents because teens tend to be influenced by what they see in the media and pop-culture. Informative and positive media campaigns may reduce the negative effects of other forms of mass media that may instigate teen dating violence or other risky behaviors (22). Youth are also influenced by the environment in which they live. Therefore, attempts at educating youth should extend past the use of media to include the family, schools and community programs. A multi-dimensional approach between pediatricians, families, schools, and communities would be the most effective strategy towards prevention of suicide attempts in adolescents (6). This multi-dimensional approach should include as stated, education, but also include attempts to get youth involved in positive programs that will make them feel connected to the community, enhance their sense of self and reduce involvement in risky behaviors and past-times. Sports and art, music, or drama programs are examples of some positive activities that families, schools, and communities can offer youth to prevent negative behaviors that may lead to dating violence and suicidality.

Future research on this very important topic should focus on longitudinal studies so that a causal relationship between dating violence and suicidality might be better understood. Mediating factors (i.e., medical problems, depression, and substance use) should also be examined due to their role in adolescent suicidality and violence. Identifying all risk factors for dating violence and suicidality is essential for implementing effective intervention strategies.

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Section IV: **Post-traumatic stress disorder**

11 Post-traumatic stress disorder, medical illness and suicidal behavior

Yuriy Dobry and Leo Sher

Post-traumatic stress disorder (PTSD) is concerning because of not only the severity and chronicity of its symptoms – including distressing nightmares, flashbacks, anxiety attacks, and maladaptive patterns of avoidant and nearly paranoid behavior – but also the wide spectrum of clinical and social impairments it is tightly associated with. The most striking example of clinical morbidity associated with PTSD is the well-known increase in the risk of suicidal behavior. Given that PTSD and medical illnesses increase the likelihood of suicide separately and independently, it is reasonable to suggest that the risk of suicidal behavior differs between patients suffering from PTSD comorbid with medical illnesses and patients having either condition alone. The available data point toward a novel clinical notion – an altered risk of suicidal behavior in patients suffering from comorbid PTSD and medical illnesses. This area of overlap between medicine and psychiatry is still in its infancy, with many unanswered questions about the rate, patterns, and psychobiological mechanisms of suicidal behavior in this patient population. The positive association between PTSD, medical illness and suicidal behavior that appears to exist in adult population, most likely affects the pediatric population as well. Closer investigation into the significance of the association between chronic medical illnesses, PTSD and suicidality in children, adolescents, and adults is necessary.

11.1 Introduction

Post-traumatic stress disorder (PTSD) is a set of pathological, emotional, and behavioral responses to severe trauma, which are often associated with a sense of helplessness and loss of control (1, 2). This disorder can be triggered by a wide range of traumatic events – war related violence, school bullying, or even parental neglect (1). Consequently, it is widely prevalent. Upto 6% of men and 14% of women in the US are expected to be diagnosed with PTSD in their lifetimes (1). Additionally, the return of massive numbers of traumatized combat veterans from wars in Iraq and Afghanistan is anticipated to bring with it a tidal wave of patients with new onset PTSD.

Unfortunately, PTSD is a relatively novel diagnosis, known only superficially to the general public, and is often underdiagnosed by the clinicians in every field of medicine, including mental health (3, 4). Nevertheless, the illness has progressively been recognized for its role as one of the most prevalent and debilitating psychiatric conditions. Such recognition is necessary for clinical, academic, and social resources to be allocated to the understanding, treatment, and prevention of PTSD, which is considered one of the most individually debilitating and socially costly psychiatric conditions for reasons explained below.

11.2 PTSD and suicidality

PTSD is concerning because of not only the severity and chronicity of its symptoms – including distressing nightmares, flashbacks, anxiety attacks, and maladaptive patterns of avoidant and nearly paranoid behavior – but also the wide spectrum of clinical and social impairments it is tightly associated with (5, 6). The most striking example of clinical morbidity associated with PTSD is the well-known increase in the risk of suicidal behavior (7, 8). Of all individual anxiety disorders, only PTSD is strongly and independently associated with suicidal ideation and suicide attempts, as revealed by Sareen et al (9) using a large, civilian sample from the US. Moreover, PTSD is strongly correlated with suicidal behavior, as shown in the 50-article meta-analysis by Krysinska et al (10).

11.3 PTSD, medical illness and suicidality

The relationship between PTSD and suicidal behavior appears to be more complex than a simple, direct correlation. A growing amount of data indicate PTSD not only carries a strong, independent risk for suicidality but also is frequently comorbid with a number of medical conditions (11, 12). For example, respiratory, cardiovascular, neurological, and rheumatologic disorders, each of which constitutes an independent risk factor for suicidal behavior (as evidenced by data from hospitalized patients with medical illnesses, who demonstrated greater than eight times the rate of suicide of the standardized general population (13).

Given that PTSD and medical illnesses increase the likelihood of suicide separately and independently, it is reasonable to suggest that the risk of suicidal behavior differs between patients suffering from PTSD comorbid with medical illnesses and patients having either condition alone. The first line of evidence that supports this idea is a study by Freeman et al (14) who used a general health survey to examine patients with PTSD in terms of self-reported assessments of physical functioning. Interestingly, they found that military veterans with PTSD and a history of suicide attempts scored lower in such categories as vitality, bodily pain, and general health perception than matched controls without histories of suicidal behavior. These results suggested that poorer general health status and lower perception of physical health are associated with a higher risk of suicidal behavior in patients with diagnoses of PTSD. Additionally, the demonstration that negative self-perceptions of health might be positively correlated to a risk of suicidality in this patient population hints at a potential psychological mechanism of these findings.

Further evidence on the relationship between PTSD and suicidal behavior is provided by Brenner et al (15) who studied patients with comorbid PTSD and traumatic brain injury (TBI). They statistically demonstrated that the risk of suicidal behavior is significantly higher in patients with comorbid PTSD and TBI than in patients diagnosed with

TBI only. Even more evidence is provided by Barnes et al (16) who found that mild TBI increases the severity of PTSD symptoms in patients suffering from the co-occurrence of these disorders, possibly increasing the risk of suicidal behavior in this population indirectly. These findings further suggest an interplay between TBI and PTSD that might alter the risk of suicide. Providing additional evidence that the interaction between symptoms of medical conditions and those of PTSD can potentially augment the risk of suicide, another study demonstrated that cancer patients with acute stress disorder (a syndrome similar to PTSD) had an increased risk for suicidal ideation compared with cancer patients without ASD (17).

11.4 How PTSD and medical illness interact to influence suicidal behavior?

From an examination of the above findings, two relationships emerge: medical disorders are more common among PTSD sufferers than in the general population, and this co-occurrence appears to pose a unique risk for suicidal behavior when compared with the independent risks inherent to both PTSD and medical conditions. To the best of our knowledge, however, the psychobiological mechanisms governing these comorbidities and the altered suicide rates associated there with have not been adequately investigated. We propose several possible ways in which PTSD and medical illness might interact to influence suicidal behavior, regardless of the cause-and-effect relationships between the two diagnoses (whether PTSD precedes a medical illness, or results from it). First, PTSD from some, initial traumatic event may become exacerbated by a new onset of PTSD symptoms caused by a medical illness, and this interaction could modulate the risk of suicide. Second possibility is that the symptoms of anxiety or mood disorders, which are associated with numerous medical diseases, might augment the risk of suicidal behavior in patients suffering from PTSD. Finally, neurological, endocrine, and immune abnormalities known to be associated with various medical disorders might influence PTSD symptomology (and consequently, the risk of suicidality). For example, the hypothalamic-pituitary-adrenal axis and several immunomodulators have been shown to play critical roles in chronic, severe diseases such as cancer and diabetes, as well as in PTSD (18, 19).

The available data point toward a novel clinical notion – an altered risk of suicidal behavior in patients suffering from comorbid PTSD and medical illnesses. This area of overlap between medicine and psychiatry is still in its infancy, with many unanswered questions about the rate, patterns, and psychobiological mechanisms of suicidal behavior in this patient population. For instance, does the risk of suicide increase, decrease, or remain unchanged after the addition of a particular medical comorbidity in PTSD patients, and is the change additive or synergistic? How do the risks of suicidal ideation, suicide attempts, and completed suicide differ between a person in whom medical illness caused PTSD and a person who experienced PTSD

before a medical illness? Finally, can biological markers in this patient population provide some clues regarding the mechanism of altered suicide risk, and can these markers serve as targets for therapeutic agents? Regardless of the underlying mechanism of the risk of suicidality in patients with comorbid PTSD and medical illnesses, future studies need to address the above questions with the goal of devising better approaches to screening and treatment, given the medical, social, and economic implications of suicide.

11.5 Implications for children and adolescents

The positive association between PTSD, medical illness and suicidal behavior that appears to exist in adult population, most likely affects the pediatric population as well. Thus, it is an extraordinarily alarming but very poorly understood overlap between the fields of pediatric medicine and psychiatry that deserves serious academic attention. The following studies underscore the link between PTSD, medical conditions and suicide in children and adolescents. Stuber and colleagues (20) demonstrate in their paper that PTSD is tightly associated with pediatric medical illness, and is often a psychiatric product of a physical disease. Seedat et al (21) investigated medical comorbidities in female children and adolescents with PTSD in a cross-sectional, epidemiologic case-control analysis and showed that PTSD is associated with adverse health outcomes affecting almost every organ system, both in children and adults. At the same time, Vajda and colleagues (22) showed through a retrospective medical record review that adolescent patients with chronic medical conditions and illness are more likely to have a history of repeat suicide attempts. Finally, Lipschitz and colleagues (23) described clinical correlates of PTSD in over 70 adolescent (aged 11.1–18.3 years) who were assessed using a structured diagnostic interview. Male and female adolescent subjects diagnosed with PTSD were significantly more likely to have attempted suicide and report greater depressive and dissociative symptoms. Closer investigation into the significance of the association between chronic medical illnesses, PTSD and suicidality in children and adolescents is necessary. We recommend a broad based, multidisciplinary approach to the academic and clinical aspects of this relationship.

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12 Prevention of suicidal behavior in adolescents with post-traumatic stress disorder

Eugene Ruby and Leo Sher

Post-traumatic stress disorder (PTSD) is significantly associated with an increased risk for suicidal behavior among adolescents. Suicide is one of the top three causes of adolescent deaths worldwide. Despite the strong relationship between PTSD and suicidal behavior, precise causal pathways linking PTSD to suicide in adolescents remains unclear. A slew of mediating factors and variables commonly present themselves with both suicide and PTSD, including comorbid psychiatric disorders, exposure to different forms of trauma and stressful life events, core neurobiological changes, and mental, emotional, and physiological states like hyperarousal, impulsivity, and aggression. Because youth is such a critical stage of development, it is very important that at-risk adolescents are identified and referred for treatment. With many treatment challenges in these populations, effective implementation and use of prevention methods are of increasing importance. The most proven prevention methods include physician education, means restriction, and gatekeeper training. Other strategies that have received empirical support are public education campaigns and implementing guidelines for the media, including those for television, print media, and the Internet.

12.1 Introduction

A 2010 report, using the National Comorbidity Survey-Adolescent Supplement, found the lifetime prevalence of post-traumatic stress disorder (PTSD) in 10,123 adolescents aged 13–18 years to be 5% (and 7% for those aged 17–18 years) (1). A 1999 literature review found this number ranged from 3.5–8.1% for adolescents, compared with adult populations which exhibited figures as low as 0.8–1.2% (2). Adolescents are at a particularly high risk for experiencing traumatic events (3) and developing PTSD as a result of these experiences (4). This is especially worrisome because youth is a critical stage of development, and having PTSD can hinder maturation and identity formation and lead to life-long deficits with necessary mental and emotional skills (2).

Post-traumatic stress disorder is significantly associated with an increased risk for suicidal behavior (5, 6), though this association has been much less researched than the relationship between suicidal behavior and other disorders known to be risk factors, like major depression and substance-use disorders (7). One study found that among 3,021 adolescents and young adults, aged 14–24 years, who made past suicide attempts, PTSD corresponded with a higher risk for suicide attempts than any other psychiatric illness (8).

According to the World Health Organization (WHO) (9), suicide is one of the top 3 causes of death among those aged 10–24 years. About 4 million adolescents attempt suicide every year and more than 100,000 of attempters successfully take their own life, resulting in one youth suicide every 5 minutes around the world (10). Annually, suicides are responsible for 1.6% of all deaths in the US, but 15.6% of deaths among those aged 15–24 years (11). Judging by the fact that suicide is extremely difficult to predict in the clinical setting (12), focusing a great deal of effort on preventing suicidal behavior outside of the clinical setting is of the utmost importance (e.g., limiting access to lethal means or implementing guidelines for the media to follow when reporting about suicides). The purpose of this review is to discuss and critically analyze prevention methods for suicidal behavior in adolescents with PTSD.

12.2 PTSD and suicidal behavior in adolescents

More than 90% of youth suicide victims have at least one diagnosable psychiatric disorder at the time of death (13). Seventy-five percent of those with PTSD have other mental health problems (14). Comorbidity of PTSD with other psychiatric conditions (like mood disorders, substance-use disorders, and psychosis) is associated with an increased suicide risk and higher rates of suicidal behavior (7). Depression is the most prevalent disorder among youths who have taken their own lives (13, 15). Taken together, this might lead one to consider a few of the (many) possibilities of causal interaction between PTSD and suicidal behavior; certain PTSD symptoms cause depression, which in turn leads to suicidal behavior or even that specific attributes or symptoms common to all or some of the disorders mentioned above (such as sleep disturbances) independently predict suicidal behavior (7). However, with so many variables and risk factors to take into account, the causal chain of events linking PTSD and suicidal behavior remains unclear. As a number of studies have pointed out, while almost all suicide victims have at least one psychiatric disorder, most patients who have only one or more psychiatric disorders (without any other risk factors) do not actually commit suicide (16). Thus, in mapping out possible avenues of causality between PTSD and suicide, all other risk factors for suicide that might play a role must be taken into account.

There is some evidence that PTSD can be an independent risk factor for suicidal behavior (17, 18). For example, a cohort study of 1,698 young adults who grew up in Baltimore revealed a significantly increased risk of suicide attempts for those who had PTSD compared to those without the disorder and those who experienced a traumatic event without developing the illness; and this increased risk remained unchanged even after adjusting for some other notable risk factors, like depression and sex (17). Research conducted by Mazza on 106 adolescents in grades 9–12 revealed that PTSD symptomology was significantly related to a heightened risk of suicidal ideation after adjusting for depression and gender (18). Unfortunately, these studies failed to

control for a sufficient amount of associated risk factors, like childhood sexual abuse, in order to rule out the effects of confounding variables that were not statistically analyzed in these studies.

It is also possible that trauma and stressful experiences can lead to suicidality without a mediating PTSD diagnosis. Traumatic and stressful events, such as exposure to terrorism and physical and sexual abuse have all been found to be risk factors for PTSD, suicide, or other suicidal behaviors (19–21). However, the cohort study that was already described (17) found that only PTSD, and not traumatic experiences, independently predicted suicide attempts. Also of important note in this study was the finding that PTSD caused by trauma that involves assaultive violence was significantly associated with suicide attempts, whereas PTSD caused by trauma that did not involve assaultive violence was not significantly related to suicide attempts. This finding may suggest a differential association between suicidal behavior and the type of trauma experienced.

One way of assessing the association between suicide and PTSD is to focus on some of the specific symptoms of PTSD that might be risk factors for suicide. One study found that increased levels of hostility, depression, and arousal were related to higher suicide risk (22). Hostility and increased arousal fall within the hyperarousal cluster of PTSD symptoms. However, levels of avoidance (avoidance cluster) were negatively correlated with suicide risk, leading the authors to hypothesize that avoidance may serve to lessen the chances of suicide. In a longitudinal study, Sourander and colleagues looked at a group of 580 adolescents and found that those who exhibited aggressive behaviors (which fall into the hyperarousal cluster) at age 8 were significantly more likely to show suicidal behaviors (specifically, suicide attempts and suicidal thinking) 8 years later, at age 16 years (23). Impulsivity (associated with the hyperarousal cluster) has also been documented to have strong ties to both PTSD and suicidal behavior. For example, Kotler and colleagues found a positive association between impulsivity and risk of suicide in patients with PTSD, as compared with matched controls, who showed no association between these two factors (24). Given the fact that the majority of suicidal crises are short-lived, unplanned, and associated with ambivalent feelings of whether to live or to die (25), impulsivity seems to be an especially strong link between PTSD and suicide. The re-experiencing symptom cluster of PTSD has also been positively associated with PTSD and suicide (26). With regards to the efficacy of different coping strategies, Amir et al documented that in PTSD patients, psychological coping mechanisms like minimization, mapping, and replacement were associated with lower risk of suicide, and that suppression was associated with an increased risk of suicide (27).

Other risk factors for suicide include gender, a family history of suicide, and past suicide attempts. Men successfully complete suicide more often and tend to use highly lethal means, as compared with females who attempt more suicides using low-lethality procedures (20). A family history of suicide and previous suicide attempts are two of the most significant risk factors for suicide (28). A family history of suicide may increase the

chance of developing PTSD (29) and previous suicide attempts are potentially traumatizing experiences in and of themselves. Having a family history of suicide or having a history of suicide attempts can also potentially lead to contagion-like effects.

Contagion, a phenomenon by which interpersonal contact with suicidal individuals results in the spread of suicidal behaviors (with suicide methods often being mimicked or imitated), sometimes throughout entire communities, is more common among youth than among those in other age groups (13, 29). A special type of contagion called the Werther effect refers to copycat suicides spurred on by media coverage of people taking their own lives. Media induced contagion effects will be discussed in detail later on.

In terms of neurobiological underpinnings, serotonergic abnormalities are a common finding in post-mortem analyses of the brains of suicide victims (16, 30). Compared with those who die of causes other than suicide, suicide victims are generally found to have lower levels of pre-synaptic serotonin transporter sites in various brain regions, including the hypothalamus, the brainstem, the prefrontal cortex, and especially in the ventral medial region of the prefrontal cortex (31, 32). Suicide victims also tend to have higher levels of 5-HT_{1A} post-synaptic receptors, with this also being most evident in the ventral medial prefrontal cortex (31). The ventral medial prefrontal cortex is associated with executive functioning, so impairment of this brain region may result in deficits in the ability to inhibit distressing, aggressive, or suicidal emotions, and thus lead to more impulsivity (16, 30). As mentioned, impulsivity and aggression are strongly linked to both PTSD and suicidal behavior. Reduced levels of the principal metabolite of serotonin, 5-HIAA, in the cerebrospinal fluid have been consistently observed in both those who have committed suicide and those who have attempted suicide (16, 30, 33). Amongst suicide attempters, 5-HIAA has been reported to be negatively correlated with the lethality of the suicide attempt (30). Decreased serotonergic activity has also been observed in victims of childhood abuse (16) and other traumatic experiences, as well as in patients with PTSD. One recent study (34) found that patients with PTSD had significantly reduced levels of serotonin 1B receptors as compared to those without PTSD. Furthermore, those who were exposed to traumatic experiences without developing PTSD also had lower levels of serotonin 1B receptors (though levels were not as those with full blown PTSD). Perhaps the most important evidence for serotonergic abnormalities in PTSD patients is the relative effectiveness of selective serotonin reuptake inhibitors (SSRIs) in the treatment of this disorder (35). In terms of the prefrontal cortex, imaging studies have revealed lower levels of activation in the medial prefrontal region when patients with PTSD are presented with various stress-inducing stimuli (36, 37). These deficits may lead to some of the symptoms and behaviors associated with PTSD, like aggression, impulsivity, depression, heightened startle response, and suicidal behavior. Also, when taken alone, these symptoms and behaviors are indirect evidence of serotonergic impairments, as well as prefrontal cortex deficits (35).

Trauma, PTSD, and suicide have all been associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (16, 29). As suggested by animal models using maternal deprivation procedures, hyperactivity of the HPA axis (including physiological alterations like elevated glucocorticoid levels and increased sensitivity to stress) appears to be linked to traumatic experiences (38, 39). Surprisingly, PTSD is frequently associated with an increased inhibition of the HPA stress response and average or reduced levels of cortisol (40). However, as Yehuda explains, it is not necessarily the case that individuals with PTSD display lowered HPA and stress and stress responsiveness (40), as indicated by reports that increased cortisol and HPA responses are exhibited by individuals with PTSD who are exposed to reminders of traumatic events (in comparison with controls) (41, 42). Some of these contrasting findings might be explained by individual differences in genetic predisposition, the type of trauma experienced, or the age at which trauma is experienced. A much more consistent finding in the literature is a reduced hippocampal volume, which is considered a core feature of PTSD (29). Because memory, learning, and fear conditioning are highly dependent on the hippocampus, damage to this brain area may play a role in PTSD by causing traumatized individuals to over-generalize fear responses associated with their traumatic experiences to novel environments or people and exhibit hypervigilance and stressful reactions in even the safest of situations (29). Overactivity of the amygdala, as shown in patients with PTSD who are presented with stress-inducing stimuli (43, 44), may also help to explain such fear and stress responses. Taken together, these deficits can cause symptoms related to both PTSD and suicide, such as helplessness, aggression, negative expectations, low self-esteem, and self-destructiveness (16, 29). The HPA axis also has connections with the sympathetic nervous system via the hypothalamus, where fear signals are passed along. Overactivity of the sympathetic nervous system, as evidenced by heightened norepinephrine responsiveness to perceived threat, and elevated heart rate and blood pressure, is also associated with the hyperactivity of the stress response (35). Furthermore, abnormalities in neurotransmitter systems associated with controlling and mediating the stress response such as the neuropeptide Y, endogenous opioid, gamma-aminobutyric acid (GABA), and glutamate systems have also been linked to PTSD and the dysregulated stress reaction associated with sensitization (29).

Finally, it may be the case that PTSD, suicide, and other associated conditions all share a similar genetic, epigenetic, and/or neurobiological predisposition (16, 29). For example, genetic and neurobiological differences associated with sex may play a role in predisposing someone to PTSD and suicidal behavior. As previously mentioned, women commit suicide less often than men do. Women have been reported to exhibit higher levels of 5-HIAA in the cerebrospinal fluid as compared to men (45). Thus, sex may represent a predisposition towards higher rates of both suicide and PTSD in men because these disorders are associated with hypoactivity of serotonergic functioning. What seems most likely is that these disorders are caused by a mixture of

both a shared underlying predisposition and deficits acquired after the development of PTSD (or other common comorbid conditions).

12.3 Prevention

There has been a good deal of research conducted on suicide prevention for the general population and also some dealing with suicide prevention in adolescent populations. However, there have been no empirical investigations of prevention methods tailored to suicidal adolescents with PTSD.

There are two general options when it comes to suicide prevention: decreasing risk factors for suicide or case finding, which refers to looking for and identifying at risk persons for referral and treatment (5). A literature review by Mann et al found that the three most effective prevention techniques have proven to be means restriction, education of primary care physicians, and gatekeeper training (46).

12.3.1 Means restriction

Means restriction refers to any measures taken to decrease access to or availability of suicide means (24). Suicide attempters tend to use specific, favored methods, and when they are unable to attain the means for these favored methods, they are less likely to make a suicide attempt (47).

The main justification for implementing means restriction measures is that the majority of suicidal crises and feelings of wanting to kill oneself are brief and transient, unplanned or impulsive, and often accompanied by mixed feelings of whether to live or to die (24). Thus, with more lethal means unavailable or inaccessible during this short window of opportunity, the suicidal person will either not go through with the attempt or use less lethal means (24). Given the evidence that impulsivity may serve as a strong link between PTSD and suicide, means restriction seems as if it might be just as effective if a suicidal crisis is spurred on by PTSD-related impulsivity or other PTSD symptoms associated with suicide.

According to the Centers for Disease Control and Prevention (CDC), the top three methods used by young people in suicides are firearms (45%), suffocation (40%), and poisoning (8%) (48). One study found that across US, suicide rates are higher for people living in locations where there are more guns in homes and that this association is most prominent for adolescents aged 5–19 years (49). In support of means restriction, studies consistently show that passing firearm control laws lead to reductions in suicide rates (50, 51). For example, the passing of gun control legislation in 1976 in the District of Columbia led to a 23% reduction in firearm-related suicides (50). Similarly, gun control laws in South Australia led to significant decreases in suicides using firearms, in comparison with other Australian states without similar gun

laws in place (where there was an increase suicide rates) (51). For suicidal adolescents with PTSD, one potentially beneficial future avenue for research might be to focus on figuring out if PTSD caused by certain types of trauma leads to using specific suicide means or methods more often than others. For example, it seems reasonable to think that those who experience gun-related trauma might be less likely to choose firearms as their means because they will probably seek to avoid any reminder of the trauma at the risk of triggering re-experiencing symptoms. The finding that avoidance behaviors are negatively correlated with suicide risk (22), might provide some support for this hypothesis.

12.3.2 Physician education and training

One of the most promising prevention methods of suicide in adolescents is to educate and train primary care physicians to better screen, identify, and treat patients with psychiatric disorders, as well as to refer such patients to mental health care professionals (46). However, an excessive amount of physicians fail to identify and effectively give much needed support or treatment to patients with suicidal inclinations and associated psychiatric disorders, like depression (15). This failure to recognize depression and other risk factors related to suicide may be a major reason why most suicide victims go untreated before taking their own lives (46). Physician education may be of particular importance in children and youth because it is often the case that physicians are a youth's only source of mental health care service (52). The prevention of suicide in the primary care setting can potentially be an extremely effective method because about 75% of all victims have contact with a physician within a year of suicide and almost half of all victims have contact with a physician within a month of taking their own lives (53). In one study based in Australia, primary care physicians took part in a training workshop that was intended to help them to better identify and effectively respond to young people at risk for suicide. Despite the fact that the workshop only lasted for one day, identification of suicidal patients increased by 130% (54). Other studies also show that this prevention method leads to reductions in suicide rates and increases in rates of identifying those at an elevated risk for suicide (55, 56).

Physicians should screen all adolescents to assess coping skills and any thoughts or behaviors, past and present, which are associated with suicidal behaviors (57). With regards to helping suicidal adolescents with PTSD, physicians should also be adept in screening for, identifying, and triaging adolescents with PTSD (and other disorders related to increased risk of suicide). The Society for General Internal Medicine enlisted the help of the American Association of Medicine and Psychiatry, the American Psychiatric Association, The American College of Physicians, and the American Academy of Physician in order to provide physicians with literature and guidelines to effectively diagnose and treat psychiatric disorders commonly

observed in primary care (58). Furthermore, physicians might also want to assess which type of trauma led to PTSD for different individuals so as to understand avoidance patterns and to get a grasp on which suicide methods might be most favorable for each individual. Taking screening and assessment results into account, the clinician can also serve to form a support system for the youth patients by opening lines of communication with parents and other adults and potential gatekeepers in the local community, including teachers, activity partners, etc. (59). In general, by forming respectful, encouraging, and most importantly, understanding relationships with adolescent patients, primary care physicians can open a much needed line of support for adolescents in times of crisis or distress (59), which would be especially useful for those suicidal youth with comorbid or particularly distressing disorders, like PTSD and depression.

Screening instruments, which may focus on risk factors for suicide or suicide alone (46), are valuable tools that physicians should utilize. These instruments reliably lead to accurate recognition of and significantly higher detection rates of at-risk youth populations (60, 61).

12.3.3 Mental health care

Of all of the many varieties of therapies that are typically utilized in an attempt to treat suicidal people, dialectical behavioral therapy is the only one that has continuously proven to be effective in lessening suicidal behavior in the adult population (20). Unfortunately, none of the research found on this topic has focused any attention specifically on suicidal behavior in adolescents with PTSD. With specific regards to coping strategies, clinicians should teach and encourage PTSD patients to use coping strategies associated with lower risk of suicide in PTSD patients, like replacement, mapping, and minimization, and to avoid those associated with higher risk of suicide in PTSD patients, like suppression (25). According to Sher and Ganz, a combination of pharmacotherapy and psychotherapy is likely to be the best treatment option for mental health professionals to give to adolescents with PTSD (29).

12.3.4 Gatekeeper training

Gatekeeper training refers to educating and training adult community members who communicate and interact with adolescent populations on a day-to-day basis to recognize youth at risk for suicide, assess their level of risk, and refer them to mental health professionals for treatment when necessary (46). Examples of potential gatekeepers are teachers, guidance counselors, coaches, prison and military officials, clergy and other religious professionals, police, first responders, nurses, primary

care physicians, and social workers (46, 62). Unfortunately, many potential gatekeepers lack either knowledge of the risk factors for youth suicide or do not possess the appropriate attitudes or intervention skills to effectively take action when needed. For example, a nationwide survey of US high school teachers showed that fewer than 10% of all teachers felt that they could identify at-risk students, and even amongst counselors who possessed knowledge of the risk factors; two thirds did not think that they could recognize students at risk for suicide (63). It becomes even more important to contrive gatekeeper strategies when one takes into account a finding by Wyman and colleagues: of a mixed sample of 2,059 8th and 10th grade students surveyed with regards to help-seeking attitudes, those who mentioned a past suicide attempt were much less likely than those without a past suicide attempt to seek help or believe that any school personnel could help them (64).

The cumulative literature on this topic has not yet proven gatekeeper training to have an independent or significant effect on diminishing suicidal behavior (62). However, there have been some reports that point towards positive effects of these training programs.

A study based in Quebec (65) gave gatekeeper training to 43 adult “helpers” who worked with youth populations. Within 6 months of the training date, over 60% of the helpers made an intervention with a suicidal youth, and the adults given the training attained increased intervention skills and knowledge of suicidal behavior as compared with 28 helpers in a control group who didn’t receive the training.

12.3.5 Public education programs

Public education programs attempt to provide suicide awareness information and inform the public about risk factors and identification strategies, as well as to help cultivate appropriate attitudes towards suicide and suicidal behavior. These programs are often targeted at adolescent populations (13) and especially in the school setting (28). In one study, a school-based education campaign was utilized. Adolescents participated in meetings that focused on opening them up to inner conflicts and negative life experiences associated with suicidal behavior, as well as promoting positive coping mechanisms to help them to deal with distressing feelings and emotions. Results showed that because of the intervention, students were able to cope more effectively with stress and negative feelings like hopelessness (66). Hopelessness is a symptom associated with both PTSD and suicidal behavior in adolescents. However, there is not enough empirical evidence investigating the efficacy of this method of suicide prevention to make any definite conclusions or recommendations (28, 46). Such preventative interventions can also aim to target more specific at-risk populations like suicidal adolescents with PTSD by including information about identifying individuals in this population, risk factors, and treatment options.

12.3.6 Media guidelines

As evidenced in the literature, the media (print, television, internet) can help to facilitate reductions of youth suicide by providing supportive advice and educating the public or can have potentially disastrous outcomes, invoking mass contagion effects as a result of irresponsible coverage of suicides (e.g., romanticizing or glamorizing suicide, or dramatizing more lethal suicide methods) (24, 46, 67–69). Improper coverage can even lead to the teaching of new or alternative suicide methods (24), as well as draw attention to suicide hot spots (70). In this context, the effects of contagion can be far more calamitous than contagion via person-person contact in community and local settings (as already discussed) (67). Furthermore, there is good evidence that youth populations are at the greatest risk to media-related contagion effects (68, 71): Phillips and Carstensen (68) reported that TV news and feature stories about suicide caused significant increases in teenage suicide over the week following these broadcasts (almost a 7% increase) compared with adult suicides that increased by less than half of a percent. In addition, broader coverage of these stories by more news stations led to higher numbers of teen suicide. It should be noted that because this study took place in the US, the generalizability of these results to other countries (where the impact of TV news might be different) is unknown.

Media contagion (also commonly referred to as the “Werther effect”) can in large part be explained by social learning theory (67). In the case of the Werther effect, greater public attention can serve as a reward to the observer and can present as longer duration of coverage, greater amounts of coverage (67), and greater prominence of coverage, including front page placement or covering celebrity suicides (72). Furthermore, observers are more likely to model behavior off of others that they share similar characteristics with (like age or gender) and maintain more attention on viewing stories that involve such people (73, 74). For example, for upto 70 days after the showing of a weekly serial that depicted the railway suicide of a 19-year-old male student, the number of railway suicides was highest amongst the population of 15–19-year-old males (with rates increasing by upto 175%), as compared to all other age/gender populations (74).

There are also a few studies looking into the potential relationship between PTSD and media effects. Researchers dealing with 69 youths in the sixth grade who lived near Oklahoma City when the 1995 bombing took place, but were not directly exposed to the event, found that indirectly witnessing the event via media sources was significantly associated with acquiring PTSD symptoms (75). Another study based in Ontario studying 143 undergraduate students (aged 17–37 years), looked at the PTSD symptomology related to media exposure to the 9/11 terrorist attacks. Media exposure was significantly associated with two of the three PTSD symptom clusters, including hyperarousal and re-experiencing symptoms, but was not associated with the avoidance cluster (76). Taken in light of results already mentioned, that PTSD symptoms like hyperarousal

and re-experiencing symptoms in youth lead to an increased risk of suicide, it can be inferred that media coverage of certain events can serve to heighten these risk factors even more and create an even shorter bridge between PTSD and suicide.

As already briefly mentioned if conducted in a responsible manner, media reports on suicide can have potentially beneficial effects (the Papageno effect). The main prevention method for suicidal contagion and other adverse effects of the media is providing reporting guidelines for media organizations to follow (46, 77). Such guidelines may include avoidance of sensationalizing or dramatizing suicides, encouraging suicidal people to seek treatment and care, and educating them about the risk factors and effective coping mechanisms, educating those involved in the production and reporting about contagion, avoidance of elaborating on specifics of suicide methods or hot-spots, and limiting the coverage and prominence of suicide cases and avoiding front page placement (67). These guidelines listed are some that help to form a set of national guidelines developed by the American Foundation for Suicide Prevention (78). The Centers for Disease Control and Prevention has also released similar guidelines for media reporting (79). Although no research has focused on the efficacy of these specific guidelines (46, 67), there has been some work done on others. For example, in Vienna, Austria suicide rates, and in particular, rates of subway suicides, increased dramatically after the subway system was put into place in 1978. Elmar and Sonneck documented an 80% decrease in subway suicides after guidelines were developed by the Austrian Association for Suicide Prevention and spread via a media campaign in 1987 (80). In another study, after Swiss newspapers and magazines implemented a set of guidelines, researchers found that in comparison to before the guidelines, articles received less prominent placement, were not as lengthy, less sensational, and included less pictures (81). Taking into account the studies on media coverage of PTSD, similar guidelines can be put into place with minor additions to account for the risk factors and symptoms associated with suicidal adolescents with PTSD.

There have been relatively few research efforts that have looked to see if the Internet might have a relationship with suicidality (82). However, the internet is of particular concern in light of the facts that social networking sites can be utilized to spread information in just minutes (24), there are suicide chat rooms and websites containing instructions for different suicide methods (46), and almost all young Americans and adolescents have Internet access to one degree or another (with 93% of all 12–17 year olds and 89% of 18–24 year olds being online in 2009) (83).

The most used social media site, Facebook, reached 500 million registered users in 2010 (84) and in 2009, in general, social networking sites were used on a regular basis by 73% of teens, including 55% of 12–13 year olds and 82% of 14–17 year olds (85). There is evidence that Facebook and other social media sites may actually serve to increase social support and boost mental well-being (86) and even stop or decrease suicidal ideation in young people and adolescents (82). One especially worrisome online venue is websites devoted to promoting suicide by detailing information on

suicide means and methods, of which there were found to be more than 100,000 in 1999 (87). These websites suggest suicide as a solution to life's issues and contain detailed descriptions of methods yielding the maximum effect, as well as suicide notes and pictures of people who committed suicide. They exert group pressure to fulfill suicide plans, glorifying those who have committed suicide. Other potential avenues for obtaining information about suicide include forums and self-help pages, in which other users can leave comments or feedback. In 2010, Ries (88) documented a case in which a 24-year-old male posted a comment on a forum about the intention to kill himself. While some showed support and sympathy, others egged him on. The young man went on to kill himself. In terms of Internet-related PTSD effects, one study found that amongst elementary school children who indirectly witnessed or heard about the 9/11 terrorist attacks via different media outlets, children who saw or heard about it on the Internet reported more PTSD symptoms than those who witnessed the event by way of television or print media (89).

A recent cohort study (82) conducted with 719 14–24 year olds found that 59% of participants saw or learned about suicide stories on the Internet. Mental health information was also attained from the participants. Although hopelessness and knowing someone who attempted or committed suicide at baseline were both highly related to learning about suicides from social networking sites, social media was not related to increases in suicidal ideation in these groups, suggesting that these sites may actually serve to be effective mediums for social support and preventing suicidal behavior. The same beneficial effects were not observed with online forums, which were related to increases in suicidal ideation, providing evidence that forums may serve to encourage or facilitate suicidal behavior. The same goes for blogging, which was related to hopelessness. These results may indicate that youths with PTSD or other mental health problems associated with suicide may be best off visiting social media sites as opposed to forums or blogs.

Like with other types of media prevention, the Internet can also be a medium used to adequately educate adolescents about suicide, its causes, risk factors, and treatment options. In order to combat the deleterious effects of suicide-promotion sites and other harmful venues, suicide-prevention websites can be utilized to support and guide suicidal youth to teach effective coping strategies and proper treatment options (82). Furthermore, mental health providers and gatekeepers like primary care physicians and teachers can help educate youth of the dangers and benefits of Internet use. Also, as already discussed, Facebook and other social media sites may actually help to prevent suicide by allowing support and guidance from friends and other people in one's social network (13, 86). Finally, media guidelines for reporting suicide on the Internet have been put together, but thus far no research investigations have studied the effects of such guidelines (46, 78, 90). All of the fore mentioned prevention options could be utilized for suicidal adolescents with PTSD and/or other psychiatric conditions.

12.3.7 Multi-dimensional prevention methods

Given the demonstrated efficacy of most of the prevention methods discussed thus far, it seems reasonable to hypothesize that a more versatile, multi-dimensional suicide prevention method, combining all or some of these methods, might prove to have the best results of all. In a study based in Nuremberg, Germany (91) both primary care physicians and community gatekeepers (clergy, help-lines, mental health care workers, policemen, prison officers) were given suicide prevention training. Furthermore, media organizations (TV, radio, and newspaper) were given guidelines to follow concerning reporting of suicides in order to prevent copycat suicides and contagion-related effects. There was also a public education campaign launched which organized lectures for the general public and enlisted the help of public officials and various media outlets (including a cinema trailer and an internet website) to help educate community members and health care workers about depression (which of course, is one of the main risk factors for suicide) and to encourage people with depression or depressive symptoms to seek help. Results showed that over a 2-year period, there was a 24% reduction in suicidal acts (which included completed suicides and suicide attempts), and that this reduction was significant compared with the control region (Wuerzburg, Germany) that did not receive the prevention programs. In Wuerzburg, suicidal acts increased by over 7% over the 2-year span. More research needs to be conducted on such multi-dimensional approaches in order to come to any concrete conclusions about the efficacy of this method compared with the other methods discussed.

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Section V: Substance abuse

13 Attention-deficit hyperactivity disorder and dual disorders: educational needs for an underdiagnosed condition

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A wide range of comorbid psychiatric disorders overlap with attention-deficit hyperactivity disorder (ADHD) across the life span. There is a robust and complex intersection between ADHD and substance use disorders (SUD). In the present report it is aimed to review the neurobiological and other vulnerability factors explaining the comorbidity of ADHD and an addictive disorder, as well as the key aspects of the assessment and diagnosis of dually diagnosed ADHD patients. A comprehensive and systematic search of relevant databases (PubMed, Embase, and PsychINFO) was conducted to identify studies published in peer-reviewed journals until July 31, 2012, exploring the association of ADHD and SUD with postgraduate training and residency education. Across the life span, ADHD is associated with significant impairment and comorbidity. Data from epidemiological and clinical studies show a very solid link between ADHD and SUD. It is therefore very important to carefully and systematically assess for any substance use in patients with a suspected ADHD coming to initial assessment, and vice versa. Whilst there are various valid and reliable rating and screening scales, for both SUD and ADHD in adult patients with dual pathology, diagnosis cannot solely rely on any of the instruments available. The most important and effective tool in the assessment of dually diagnosed patients with ADHD and a SUD is a full and comprehensive clinical and psychosocial assessment. It is essential to actively incorporate training opportunities on the assessment, diagnosis and management of adult ADHD and dually diagnosed ADHD patients during postgraduate education residency or specialist training.

13.1 Introduction

Training in the management of addictions remains very limited in medical training as well as in postgraduate specialist education, including psychiatric residency programs compared to other major psychiatric disorders (1, 2). However, comorbidity of addictive disorders with other psychiatric disorders is extremely common (3–6). It is rather unusual to encounter an individual presenting to treatment solely with an addiction problem. Optimal treatment of dually diagnosed patients requires awareness and adequate assessment of concurrent symptoms, syndromes and disorders, and vice versa.

Attention-deficit/hyperactivity disorder (ADHD) is a complex and multifactorial neurodevelopmental disorder characterized by age inappropriate levels of inattention, hyperactivity, and/or impulsivity (7, 8). Once considered solely as a childhood disorder, the persistence of ADHD from childhood throughout adolescence into adulthood is now fully acknowledged (9). Indeed, both ADHD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Text Revision) (DSM-IV-TR) (7) and hyperkinetic disorder, as defined in the International Classification of Diseases, 10th revision (ICD-10) (10) are recognized to persist beyond childhood into adulthood, and several national and cross-national guidelines now recommend that ADHD should be recognized and appropriately treated throughout the life span (11–13). Nonetheless, many clinicians are still unaware that this disorder frequently persists into adulthood (14). A wide range of comorbid psychiatric disorders overlap with ADHD across the life span. Comorbid conduct disorders, oppositional defiant disorder, learning impairments, anxiety disorders and mood disorders are amongst the most common psychiatric disorders in children with ADHD (8, 15, 16). Similarly, depression, bipolar disorder, anxiety disorders, substance use disorders (SUD), personality disorders, or eating disorders are very frequent among adults with ADHD (4, 15, 17–22). There is a robust and complex intersection between ADHD and SUD, with important substantial societal burden and implications in daily clinical practice and research (17, 21, 23–27).

Clinicians not trained to adequately assess, identify and diagnose the disorder often overlook a highly prevalent psychiatric condition and ascribe symptoms to other disorders or personality types, therefore resulting in low recognition and underdiagnosis of ADHD, with or without a comorbid SUD, in many world regions (12, 28). The general psychiatrist and other specialists involved in the management of patients with ADHD and comorbid SUD will require a better understanding of the factors underlying comorbid ADHD and SUD, to gain effective knowledge, skills and attitudes for raising awareness and for a assessment and an accurate diagnosis of individuals with this dual disorder. In the present report it is aimed to review the neurobiological and other vulnerability factors explaining the comorbidity of ADHD and an addictive disorder, particularly in adults and older adolescents, as well as the crucial aspects of the assessment and diagnosis of dually diagnosed ADHD patients, aspects, all of them, that are key in raising awareness and improving recognition of this complex comorbidity.

13.1.1 Literature search

A comprehensive and systematic search of relevant databases (PubMed, Embase, and PsychINFO) was conducted to identify for studies published in English in peer-reviewed journals until July 31, 2012, using the following MESH terms and keywords: “ADHD,” “substance use disorder,” “residency education” and “postgraduate

training.” In addition, reference lists were scrutinized to identify and retrieve further relevant reports and studies from additional sources and scientific databases. The literature search included clinical studies/reports as well as retrospective or prospective population-based studies with children, adolescents or adults as participants. There were no restrictions on the identification or inclusion of studies in terms of date of publication, publication status, type of publication and design type. However, abstracts of presentations to specialist meetings and conferences were not included. Titles and abstracts were screened for inclusion/exclusion, and appropriateness, and full text versions were retrieved.

A total of 130 records were identified through database searches (92 from Embase, 27 from PubMed and 11 from PsychInfo). Fifteen duplicate reports were excluded from the list. Of the remaining 115 documents, 66 further reports were excluded after careful evaluation of the titles and abstracts for considering them not eligible for the purpose of the present review. Therefore, a total of 49 documents identified through database searches were included in the report.

13.2 Epidemiology

ADHD is the most frequent childhood psychiatric disorder. The estimated prevalence of ADHD in age-school children is 3–7%, as reported in DSM-IV-TR (7). Similar estimates were reported in a systematic review and meta regression analysis that reported a worldwide-pooled prevalence of ADHD for children and adolescence of 5.29% (29). Contrary to the lay belief that ADHD is a disorder exclusively of western societies, the differences in prevalence rates reported in different studies may be related to methodological aspects rather than to real geographical variations, which supports the notion that ADHD is a global disorder, independent of culture or geographical location (29). However, like other psychiatric disorders, cultural and social attitudes may influence how ADHD, particularly in adult individuals, is understood and addressed, and may play a significant role in the diagnosis and varying acceptance of the condition (28).

As revealed in longitudinal controlled studies, a significant proportion of children and adolescents diagnosed with ADHD experience persistent symptoms and functional impairments into early adulthood, so that up to 35% of children continue to meet full DSM-IV criteria, while up to 78% show persistent symptoms or impairment (17, 30–34). Symptom persistence has been associated to childhood ADHD symptom profile. Highest persistence is associated with the combined subtype, symptom severity, comorbid major depressive disorder, elevated comorbidity (three or more child-adolescent disorders in addition to ADHD), paternal (but not maternal) anxiety-mood disorder, and parental antisocial personality disorder (30, 31, 33, 34).

In adult samples, the prevalence of ADHD in general population is approximately 3–5% (4, 35). In a systematic review with meta-analysis and meta-regression of the

epidemiological data on adult ADHD, the pooled prevalence of ADHD in adulthood was 2.5% [range, 1–7.3%], although the authors of this report concluded that due to the problems of validity with DSM–IV diagnostic criteria for this disorder prevalence rates may be reduced by underestimation of the prevalence of adult ADHD (36). In any case, the estimated prevalence of ADHD is higher than other more researched psychiatric disorders like schizophrenia or bipolar disorder. These rates are even higher in clinical samples with patients with a primary SUD (23, 24, 26, 27, 37), or other psychiatric disorders (18, 22, 38, 39), as well as in studies conducted with prison inmates (40–42).

13.3 Clinical characteristics of ADHD

13.3.1 The road to DSM-IV-TR

Although the initial example of a disorder that appears to be similar to ADHD was given by Sir Alexander Crichton in 1798 (43) and the first accepted clinical descriptions of what currently is recognized as ADHD dates to 1902 when Sir George Frederic Still published in the *Lancet* his Goulstonian Lectures, a series of three lectures to the Royal College of Physicians of London (44), ADHD was not incorporated to DSM until 1968 with DSM-II, where it was named “hyperkinetic reaction of childhood” (45) and has undergone revision with each new edition of the DSM (46).

In DSM-III the disorder was renamed “attention-deficit disorder with hyperactivity,” although it distinguished a second subtype, “attention-deficit disorder without hyperactivity” for describing individuals fulfilling criteria for inattention and impulsivity but not hyperactivity (47). In contrast, with DSM-III-R the dimensions of inattention, impulsivity, and hyperactivity were merged into one, so that to qualify for a diagnosis “attention-deficit hyperactivity disorder” there had to be evidence of eight of 14 symptoms (48). However, DSM-III-R also included a diagnosis of “undifferentiated attention deficit disorder.” Finally, in DSM-IV the term used to coin these disorders was “attention-deficit/hyperactivity disorder” (ADHD), and the list of symptoms was expanded and divided into domains of inattention and hyperactivity/impulsivity (46).

In DSM-IV-TR (7) the defining feature of ADHD is a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and is more severe than what is typically observed in individuals at comparable level of development. In addition, as a disorder of childhood onset, symptoms must have been present before 7 years of age. Another requisite for the diagnosis is that some impairment from the symptoms must be present in at least two settings, consequently there must be clear evidence of interference with developmentally appropriate social, academic or occupational functioning. Finally, to make a diagnosis ADHD, symptoms cannot be better accounted for by another mental disorder or occur exclusively during the course

of a pervasive developmental disorder, schizophrenia, or other psychotic disorders. However, neither DSM-IV and ICD-10 criteria take account of age-dependent changes in terms of the number and severity of symptoms, or changes in the way that the symptoms of ADHD might present in adults, which probably is another reason for underdiagnosis and treatment of ADHD in adults (12).

DSM-IV (49) and subsequently in DSM-IV-TR (7) defines three subtypes, as follows:

- ADHD predominantly inattentive type. Individuals affected meet six (or more) diagnostic criteria of inattention (but less than six symptoms of hyperactivity-impulsivity) that have persisted for at least 6 months.
- ADHD predominantly hyperactive-impulsive type. Individuals characteristically show six (or more) symptoms of hyperactivity-impulsivity (but less than six of inattention) that persisted for at least 6 months.
- ADHD combined type. This subtype should be used when six (or more) symptoms of inattention and six (or more) symptoms of hyperactivity-impulsivity have persisted for at least 6 months.

In addition, DSM-IV-TR (7) includes two further subtypes, ADHD in partial remission, for patients who met criteria as a child but no longer meet full criteria as adolescents or adults, although continue to display some impairing symptoms, and ADHD not otherwise specified, for patients who do not meet full criteria for the disorder and it is unclear whether criteria for the disorder have previously been met.

The combined presentation is the most common of all three ADHD subtypes, both in childhood and adolescence, as well as in adulthood, followed by the predominantly inattentive type and lastly the predominantly hyperactive-impulsive subtype (7, 49, 50).

13.3.2 New DSM, more changes. What is new in DSM-5?

The upcoming DSM-5 will incorporate some important modifications in the symptom descriptions and diagnosis of ADHD, in an attempt to solve the problems with the lack of adequate validation of DSM-IV diagnostic criteria in adults, which do not reflect appropriately clinical presentations across the life span and may lead to underdiagnosis in adult populations (46, 51). One of the essential features of ADHD that has undergone revision is the age-of-onset criterion, so that the onset of impairing symptoms has been moved from age 7 to 12 years (52). Interestingly, a recent prospective study with a birth cohort of 2,232 British children have suggested that extending the age-of-onset criterion to age 12 resulted in a negligible increase in ADHD prevalence by age 12 years of 0.1% (53). Following the evidence questioning the external validity and to some extent the discriminant validity and reliability of ADHD subtypes (54–56), including data from longitudinal, comorbidity, treatment response, and clinical outcome studies suggesting that the nominal DSM-IV subtype categories are

unstable due to both systematic and random changes over time (55–57), the DSM-IV subtype model has been revised. Therefore, the three main subtypes in DSM-IV have been changed to three current presentations, with the addition of a fourth one for a restrictive predominantly inattentive presentation (52).

While maintaining the overall structure, therefore keeping the two primary domains of inattention and hyperactivity/impulsivity, and the exact wording of all ADHD criteria, another minor modification included in the next DSM-5 is the inclusion of changes in the examples in the different items, to accommodate a life span relevance of each symptom and to improve clarity (52). Finally, in addition to removing pervasive developmental disorder from the exclusion criteria, another modification to be included in DSM-5 is the recommendation, in an introductory paragraph, to obtain information from two different informants whenever possible, in contrast to DSM-IV does not specify how this data should be collected and verified (46, 58).

13.4 Interrelationship

Across the life span, ADHD is associated with significant impairment in many areas of functioning, and with important familial, societal, and personal costs, including detrimental adverse effects to the psychological and physical well-being of the individual. At a functional level, children and adolescents with ADHD have antecedents of educational problems and significantly higher rates of discipline problems, academic failure and completion rates than unaffected individuals, independently of their level of intelligence (59–62). Partly as a consequence of the executive function deficits seen in patients with ADHD of all ages, adults have more work-related problems, with difficulties in gaining and maintaining stable employment, and in productivity due to poor time management and distractibility, higher divorce rates, and reduced quality of life than matched controls (59, 62–64). Similarly, patients with ADHD are more likely to have domestic and traffic accidents, more medical emergency use, more legal problems, as well as higher psychiatric comorbidity rates across the different age ranges, including higher rates of substance use disorders (9, 16–19, 21, 22, 24, 26, 27, 37, 41, 63, 65).

13.4.1 Epidemiological evidence of the comorbidity of ADHD with SUD

SUD are amongst the most common comorbid psychiatric disorders in adolescent or adult patients with ADHD, and vice versa. Patients with ADHD have approximately a two-fold prevalence of substance abuse or dependence, compared with general population (4, 18, 24, 37, 66). Similarly, patients with a SUD have higher rates than expected of a comorbid ADHD. The majority of studies coincide that 15–25% of adults with an addictive disorder have a comorbid ADHD (23, 26, 67, 68), rates much higher

than individuals of same age from the general population. The importance of this comorbidity derives both from the strong interrelationship between the two disorders, as evidenced in many different studies and in clinical practice, as well as from the adverse social, personal and clinical consequences of this dual pathology (Table 13.1). There do not appear to exist differences between individuals with and without ADHD in the preference of the drug of choice (24, 68). Furthermore, contrary to what is often assumed, in a recent meta-analytic review conducted to obtain a best estimate of the prevalence of ADHD in SUD populations, whilst overall ADHD was present in almost one out of every four patients with SUD, a series of meta-regression analyses showed that the prevalence of ADHD was significantly lower in subjects with cocaine as their primary substance of abuse (26).

There is evidence of a lineal relationship between the severity of the symptoms of ADHD and the risk and severity of the SUD (69, 70). Studies in adult patients diagnosed with ADHD have reported rates of alcohol abuse or dependence of 17–45% (71–73). Conversely, several studies have estimated that 19–42% of patients with an alcohol use disorder have a comorbid ADHD (74–76). In adult patients with alcohol abuse or dependence a diagnosis of ADHD is associated with significantly earlier onset of harmful alcohol use, significantly higher daily alcohol consumption, more alcohol related problems, and an increased severity of the SUD (74, 76, 77) (see Table 13.1). Likewise, individuals with ADHD start smoking tobacco products at a younger age, smoke more cigarettes daily, and are two times more likely to initiate smoking and almost three times more likely to become tobacco-dependent than non-ADHD individuals (66, 69, 78–82) and have more difficulties quitting smoking than their non-ADHD counterparts (78, 83) (see Table 13.1). In addition, although early initiation of alcohol, cannabis or tobacco use is predictive of the subsequent risk of developing other substance use disorders in individuals with ADHD, tobacco is the substance with the highest predictive value (84, 85).

Patients with ADHD and a comorbid SUD have lower retention rates in addiction treatment programs, as well as lower remission rates and more chronicity of the SUD (86)

Table 13.1: Clinical characteristics and outcome of patients with ADHD and a comorbid SUD compared to patients with exclusively ADHD or a SUD

Earlier onset of substance use and abuse (23, 74, 76, 78, 79, 87)
More likely to initiate smoking and at a younger age, as well as become dependent on nicotine, and have more difficulty quitting smoking (78, 79, 83)
More severity and chronicity of the addictive disorder (23, 67, 74, 78, 86, 87, 89, 94)
A more severe course of illness of ADHD (12, 15, 86)
Less likely to achieve abstinence (15, 94)
Higher rates of poly-substance abuse (23, 78, 87)
Increased psychiatric comorbidity (17, 23, 67, 88, 94, 95)
Lower treatment retention rates (37, 86)

ADHD: attention-deficit hyperactivity disorder, SUD: substance use disorders.

(see Table 13.1). In clinical samples 10–35% of cocaine dependent individuals have a comorbid ADHD (87–89). In patients with a cocaine use disorder the coexistence of a diagnosis of ADHD is associated with an earlier onset of cocaine, as well as of tobacco, alcohol and cannabis use (87, 89), with more frequent and more severe cocaine use (87), and with more severe psychiatric comorbidity (88). The prevalence of ADHD in patients with opioid dependence is high as well, so that 19–55% of patients in methadone maintenance treatment have been reported to have a childhood history of ADHD (67, 90–93). In opioid dependent individuals, the coexistence of ADHD is associated with more and more severe adverse consequences, including significantly higher rates of comorbid SUD and of other psychiatric disorders (particularly affective disorders, anxiety disorders, or antisocial personality disorder), more severity of the SUD, more difficulties in achieving abstinence and a more severe course of the dual disorders (23, 67, 91, 92, 94) (see Table 13.1). However, cannabis is the illicit substance most commonly abused by patients with a diagnosis of ADHD (72).

Although a history of conduct disorder increases the risk (61, 95), multiple studies (24, 66, 69, 82, 96), including several systematic reviews with meta-analyses (80, 81) have evidenced that ADHD is an independent risk factor for developing a SUD during childhood and adolescence, so that children with ADHD have a two-fold risk of developing nicotine, alcohol or other substance abuse or dependence. Nonetheless, a childhood conduct disorder is the strongest predictor of differences in patterns of drug use severity (95).

13.4.2 The relationship between ADHD and comorbid SUD. Nature of the association

The association between ADHD and SUD is bidirectional. The nature and causes for this comorbidity are complex and most likely result from the interaction of various factors, including co-occurrence of other psychiatric disorders, such as conduct disorders, antisocial personality disorders or bipolar disorders (19, 69, 95, 96), or the predominance of other associated symptoms and traits like impulsivity, novelty seeking or low self-esteem (20, 42). Similarly, at least a proportion of patients with ADHD may use tobacco, alcohol or other drugs of abuse in an attempt to self-medicate the sleeping problems, the restlessness or the low mood (97, 98). The interrelationship between ADHD and SUD has been explained also through the executive dysfunction that is characteristic of ADHD and has been observed as well in adult patients with ADHD (62, 64, 99). In addition, there are solid neurobiological substrates underlying the association of ADHD and SUD (27, 100–103).

ADHD, like other developmental disorders, is the result of the complex interaction of genetic, environmental and social factors. There is evidence of a strong genetic component to the vulnerability of the disorder, with heritability ranging from 60–90% (104, 105). Thus, ADHD is often viewed as a genetically determined dysfunction of

the dopamine and noradrenergic catecholamine system (12, 100, 106). However, estimates of heritability in adults with ADHD have been reported to be consistently lower and the extent of genetic influences on ADHD in adults remains to be clarified (12, 105). Environmental factors are also likely to play a role in the etiology of ADHD, most likely by interaction with genetic components. As such, an association have been reported between maternal and paternal smoking, as well as alcohol and other drug use during pregnancy and ADHD, with a 2–4-fold increased risk of ADHD (101, 107, 108), therefore underpinning the link between ADHD and SUD.

Neurocognitive, neurophysiological and neuroimaging studies have provided evidence of functional and structural brain anomalies underlying the pathophysiology of ADHD in children and adults, including dysfunctions in the frontostriatal network, involving the lateral prefrontal cortex, the dorsal anterior cingulate cortex, the caudate nucleus and the putamen, that have key roles in executive function and attention (102, 103, 109, 110). Likewise, studies have shown deficits in the reward-motivation system in ADHD patients that might be responsible for many of ADHD related behaviors and reduced nucleus accumbens activation with hypo-responsiveness (102, 103), and a reduction in dopamine synaptic markers associated with symptoms of inattention has been shown in the dopamine reward pathway (102, 103). Indeed, the mesoaccumbens dopamine pathway, key to understand reward and motivation (111) appears to be involved as well in the motivational and reward deficits described in ADHD, and consequently with the decreased response to reward and the greater vulnerability to substance abuse in patents with ADHD (103).

13.5 Assessment

Assessment of ADHD can be challenging, particularly in older adolescents and adults not previously diagnosed, who may come to clinic for other comorbid psychiatric disorders that can cloud or complicate the diagnostic picture and symptoms of ADHD overlooked (14, 112). Like all other psychiatric disorders, the diagnosis of ADHD in children, adolescents or adults, with or without other comorbid psychiatric disorders is made by careful and in-depth clinical and psychosocial assessment conducted by a qualified health care professional with training and expertise in the diagnosis of ADHD to look for the characteristic psychopathology (12, 13, 113, 114). To be most valid and effective this comprehensive assessment has to include a full developmental and psychiatric history, as well as the individual's person's mental state and a detailed and personal, medical, behavioral, educational, employment and social history to address the possible existence of symptoms, behavioral problems, and significant impairment across the different domains and settings (13, 114). Considering the elevated heritability and the influence of other familial factors, it is also important to

inquire about the family history, particularly of ADHD and SUD, but also of other of psychiatric and neurological problems (12).

Whilst clinicians should be familiar with the various presentations of ADHD in adults, assessment of ADHD in adults and older adolescents with comorbid SUD is not solely a matter of recognizing symptoms or identifying certain traits or characteristics such as being excessively overactive or overenergetic, restless, fidgety, or easily distractible (14, 115). It involves a more comprehensive and thorough process that includes the careful examination of symptom severity and frequency, childhood onset, chronicity and pervasiveness of the disorder, and degree of impairment in major life activities (13, 112, 113). Specifically in patients with concurrent substance abuse or dependence, it will be key to determine if ADHD, the comorbid SUD, or both best explain the presenting symptoms. It is therefore important that health care professionals working with patients that commonly have an elevated prevalence of ADHD, such as those with a primary SUD are trained and well prepared to assess adequately and detect the dual disorders, and to make an adequate differential diagnosis. Although the patient appears to be the best informant, whenever possible, collateral evidence of current symptoms, and observer reports of the level of multiple domains of impairment, and the course of illness should be obtained from close relatives (13, 116).

Some authors recommend a period of a month prior to assessing the presence of current symptoms of ADHD, to obtain more reliable information and diagnosis (15). However, this is often not possible, and therefore the assessment will need to rely on a detailed history of symptoms during periods of abstinence or at a time prior to the onset of the substance use, in order to establish if these symptoms are primary or drug induced (117).

13.5.1 Screening and assessment instruments for ADHD

There are many valid and reliable screening instruments and diagnostic interviews specifically devised for ADHD, but no single psychological or biological test provide sufficient data to reliably make the diagnosis of ADHD (13, 14), and cannot be used for diagnosis without careful clinical confirmation and elicitation of the psychopathology for diagnosis (112). However, if administered properly, ADHD rating scales can be extremely helpful, both in adolescents and adults, as they help in obtaining and organizing information on the problems experienced, as well as in documenting the frequency and severity of ADHD symptoms, as well as assessing the response to treatments (14). Similarly, there are no neuropsychological tests for ADHD with sufficient sensitivity and specificity to serve as an individual diagnostic test (12), but neuropsychological tests may serve to identify particular cognitive or executive problems in patients with ADHD or specific learning disabilities co-occurring with ADHD (112).

There are many instruments from which to choose to aid the assessment of adults with probable ADHD. The most commonly used screening instruments, rating scales

Table 13.2: Most commonly ADHD screening instruments, rating scales and clinical interviews used for adults

Instrument	Informant	Criteria	Population target	Scope
Adult ADHD Self-Report Scale (ASRS) (118)	Self-report	DSM-IV	Adults	Rating scale with 18 items. The first six items are used as a screening test
ADHD Rating Scale IV (ADHD-RS-IV) (119)	Generally self for adults (parent or teacher for children)	DSM-IV-TR	Children, adolescents and adults	Eighteen items for evaluating adult ADHD symptoms
Barkley Adult ADHD Rating Scale-IV (BAARS-IV) (120)	Self-report and observer-report rating scales	DSM-IV-TR	Children, adolescents and adults	Assessment of current ADHD symptoms and domains of impairment as well as recollections of childhood symptoms
Conners' Adult ADHD Rating Scale (CAARS) (121)	Self and/or observer rated	DSM-IV	Adults	Several versions, the 30-item version (scale 0–3) is used for screening and to evaluate treatment outcome
Brown Attention-Deficit Disorder Scale (BADDSS) (122)	Clinician-rated or self-report	Over-inclusive ADHD-related symptoms	Adolescents and adults	Focus on symptoms of inattention and behaviors related to executive functioning
Wender Utah Rating Scale (WURS) (123)	Self-report	Over-inclusive ADHD-related symptoms	Adults	Retrospective assessment for the occurrence of childhood symptoms associated ADHD
Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (125)	Semistructured clinical interview	DSM-IV	Adolescents and adults	Two sections: (1) A detailed childhood and adult developmental history, and (2) Assessment of each the 18 DSM-IV criteria, in both children and adults (with the specific examples)
Adult ADHD Clinical Diagnostic Scale (ACDS) (126)	Semistructured clinical interview	DSM-IV	Adults	Retrospective assessment of all DSM-IV criteria of childhood ADHD and an expanded assessment of recent (6 months) symptoms

ADHD: attention-deficit hyperactivity disorder, DSM: diagnostical and statistical manual.

and clinical interviews for evaluating possible ADHD in adults are summarized in Table 13.2. The majority of these instruments are frequency scales that rely primarily on DSM-IV criteria. Such is the case of the World Health Organization (WHO) Adult ADHD Self-Report Scale (ASRS) Symptom Checklist (118), a self-report instrument that includes questions for each of the 18 DSM-IV items reworded to better suit adults. The first six items of the test have been selected to be used as a screening test. Specificity of this and other screening tools seem to be lower in clinical samples with high rates of psychiatric comorbid (12). The 18-item ADHD Rating Scale IV (ADHD-RS-IV) (119), based on DSM-IV-TR criteria, is another useful screening and rating instrument that has been modified to evaluate ADHD symptoms in adolescents and adults. Likewise, the Barkley Adult ADHD Rating Scale-IV (BAARS-IV) (120), an empirically developed scale, is another valid and reliable tool for assessing current ADHD symptoms and domains of impairment as well as recollections of childhood symptoms. The BAARS-IV, based on DSM-IV-TR criteria, uses both self-report and observer-report rating scales.

The Conners' Adult ADHD Rating Scale (CAARS) (121), based on DSM-IV criteria, is available and has been validated for both the observer-administered and self-rated versions. The 30-item frequency scale is used for screening and to evaluate treatment outcome. The 40-item Brown Attention-Deficit Disorder Scale (BADDS) (122) is another instrument available in clinician-rated and self-report forms to guide the diagnostic assessment process that focuses on behaviors relating to executive functioning and inattention. The BADDS was developed prior to DSM-IV-TR and addresses over-inclusive ADHD-related symptoms. The Wender Utah Rating Scale (WURS) (123) is a self-report instrument, developed to assess retrospectively the occurrence of childhood symptoms associated ADHD. Whilst the full version consists of 61 items, a shorter version with the 25 items which most strongly discriminate between adults with and without ADHD is also available. The items derive from the monograph *Minimal Brain Dysfunction in Children* (124), which are more detailed than the 18 items in the DSM-IV criteria.

The Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (125) is a semi-structured diagnostic interview divided in two blocks that can be useful tool in the diagnostic assessment. The first part consists of a detailed childhood and developmental history, that includes developmental, environmental, and medical history risk factors, as well as childhood and adult educational, occupational, and social/interpersonal histories, and health and psychiatric histories. Finally, the second part, separately evaluates the presence of each the 18 DSM-IV criteria, in both children and adults, with the aid of specific prompts and examples. The Adult ADHD Clinical Diagnostic Scale (ACDS) (126) is a semistructured clinical interview that incorporates a retrospective assessment of all DSM-IV criteria of childhood ADHD, and an expanded assessment of recent (past 6 months) symptoms that includes all 18 DSM-IV symptoms, as well as 14 non-DSM symptoms believed to be

relevant to adult ADHD, such as difficulties with planning and organization, inattention, and mood lability.

13.5.2 Assessment of comorbid substance abuse or dependence in patients with ADHD

All individuals undergoing a psychiatric evaluation should be screened for a SUD, regardless of their age, presentation, or referral source (127). This is also valid for patients with a primary ADHD, who should be closely monitored for substance abuse as well, considering the elevated prevalence of ADHD and SUD comorbidity. Diagnosis of a SUD in a patient with ADHD is based on a comprehensive psychiatric evaluation, that should include a detailed history of past and present of all substances used by the patient, including alcohol and tobacco, as well as caffeine and xanthine derivatives. It is important to obtain information on age of initiation of each specific substance, routes of administration and frequency of use, the social context in which drug use takes place, the effects of drug use on the patient's cognitive, psychological, behavioral, and physiological functioning, the social, medical, educational and employment complications attributable to substance use, and any previous treatment episodes (127, 128). In adolescents, an age-appropriate clinical and psychosocial interview should be conducted and inquire for factors that are predictive of substance abuse (129).

Several validated screening instruments that do not require extensive training or time may be helpful in the assessment of a SUD and identifying patients with ADHD who may require a more in-depth evaluation for possible substance abuse problems. Among the screening questionnaires available, some of the most commonly used include the four-item CAGE questionnaire for alcohol abuse (Have you ever felt the need to Cut down on drinking, been Annoyed by others' criticism of your drinking, felt Guilty about drinking, needed an Eye-opener drink first thing in the morning?), translated and validated in many different languages and countries (130), the 10-item Alcohol Use Disorders Identification Test, developed by an initiative of the WHO and widely used throughout the world in primary and other health care settings as part of screening and brief intervention programs (131), or the Drug Abuse Screening Test, a 20-item self-report questionnaire for commonly abused substances other than alcohol (132). Another useful tool is the Alcohol, Smoking & Substance Involvement Screening Tool (ASSIST)(133), developed by WHO as well. It is a valid screening instrument that can be used in different settings for identifying psychoactive substance use in individuals who use a number of substances and have varying degrees of substance use.

13.6 Conclusions

Considering the solid neurobiological, epidemiological and clinical link between SUD and ADHD, as well as the clinical implications and the limited efficacy of current treatment approaches for dually diagnosed patients, clinicians need to be aware that ADHD comorbidity is frequently present in substance-abusing populations, irrespective of age, gender, ethnicity and setting, and vice versa (26, 27). It is therefore very important to carefully and systematically assess for any substance use in patients with a suspected ADHD coming to initial assessment, and in those with an established diagnosis of ADHD coming for follow-up visits, particularly if they have not been previously diagnosed or there are other comorbid disorders. Likewise, it is also very important to evaluate the presence of ADHD in any patient coming for treatment with an addictive disorder. Indeed, independently of the treatment setting or of the resources available, the most important and effective tool in the assessment and diagnosis of dually diagnosed patients with ADHD and a SUD is a full and comprehensive clinical and psychosocial assessment (12, 13). Whilst there are various valid and reliable rating and screening scales, for both SUD and ADHD in adult patients with dual pathology, diagnosis cannot rely exclusively on scores in any of the assessment instruments available. It is essential to actively address and systematically incorporate training opportunities on the assessment, diagnosis and management of adult ADHD and dually diagnosed ADHD patients during postgraduate education for health care professionals, as well as during residency or specialist training for psychiatrists and other specialists who may involve in the care of dually diagnosed patients.

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14 Cannabis and youth seeking treatment for primary mood or anxiety concerns

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Cannabis use is common in youth and there is evidence that the co-occurrence of cannabis use (and other substance use) with mental illnesses predicts poorer outcomes, including suicide. The main purposes of this study were to: 1) identify rates of cannabis use and substance use disorder risk, and 2) predictors for cannabis use among youth seeking help for mood and/or anxiety concerns in a sample population pre-screened to exclude primary substance use disorders; and 3) to determine if there was an association between cannabis use and functional impairment in this sample. We investigated substance use risk as well as hypothesized predictors of cannabis use and functional impairment including demographic characteristics, socioeconomic status, trait coping style, age of onset of several risk behaviors, current use of common addictive substances, measures of functional impairment, and current psychiatric symptom severity. Results showed that approximately half of the participants were at moderate to high risk for a substance use disorder, and just over 4% appeared to have a primary substance use disorder. They also suggested an association between cannabis use and gender (male), age of first cannabis use, recent cigarette use, and functional impairment. Independently, functional impairment was predicted by inattentive coping style, depression severity and total cannabis use score. These results confirm a high risk for addictive disorders and an association between cannabis use and functional impairment in this sample. These results support the need for substance use treatment programs to optimize care wherever youth with primary mood and/or anxiety concerns are seen.

14.1 Introduction

Youth with substance use disorders (SUDs) often have problems with mental illnesses and youth with mental illnesses, including mood and anxiety disorders, often have problems with SUDs. In one study, 50% of youth with SUDs also had non-psychotic mental health problems, and youth with SUDs plus either major depressive disorder (MDD) or posttraumatic stress disorder (PTSD) had more total disorders, more substance use related problems and lower quality of life (1). Research has shown that the rates of alcohol dependence are significantly higher in people with combined anxiety and depression (2), and people (especially young males) with mood and anxiety disorders are at high risk of comorbid SUDs (3). The co-occurrence of SUDs and mental illnesses are important to detect in youth because the combination of these conditions worsens prognosis and complicates treatment (4). In addition, SUDs predispose

to completed suicide in youth and young adults (5), although in the case of cannabis use this might be mediated through other risk factors (6).

A number of studies have demonstrated that cannabis use may precipitate the onset of bipolar disorder, depression and anxiety (as well as psychosis) in genetically vulnerable youth (7). In fact, a growing body of research suggests an association between prior cannabis use and the onset of mood and anxiety disorders in youth (8–11). This is especially problematic since cannabis is the most commonly used recreational drug and rates of cannabis use remain high, at over 25%, for North American youth (12, 13).

For these reasons, we were interested in discovering the rates of SUD risk and cannabis use in a population of youth seeking specialized psychiatric evaluation and treatment for mood and/or anxiety disorders. We were also interested in whether or not cannabis use was associated with functional impairment in this population. This involved the clinical program known as the First Episode Mood and Anxiety Program (FEMAP) in London, Ontario, Canada. This is an outpatient psychiatric clinic affiliated with the London Health Sciences Centre that serves youth (aged 16–26 years) with the recent onset of primary mood and/or anxiety concerns. This program screens out and refers youth presenting with primary substance-related concerns to a specialized SUD program in the community. However, it was noted by clinicians at FEMAP that cannabis use was common in spite of this pre-screening.

The current study sought to clarify the prevalence of youth at risk for SUDs within this psychiatric service aimed at youth clinically pre-screened not to have primary SUDs. It also sought to understand some of the associated features of youth cannabis use, and whether or not cannabis use was predictive of degree of functional impairment. Based on our clinical experiences, we believed that higher cannabis use would be associated with certain demographic features as well as some traits, life experiences and psychiatric symptoms. These included gender, age, socioeconomic status, inattentive and maladaptive coping style, age of first exposure to risky behaviors, rates of current substance use, and severity of psychiatric symptoms. Understanding the associations with cannabis use in this population could help to clarify the need for addiction specialists within primary care as well as within specialized mood/anxiety clinics for youth.

14.2 Our project

All clients coming to FEMAP between October, 2009 and July, 2012 were invited to participate in the research since the inclusion and exclusion criteria for a clinical assessment at FEMAP were identical to those for the research study. Participants were provided with information about the study, had all their questions answered, and then signed written, informed consent if willing to participate. The study was approved by the Human Research Ethics Board affiliated with the London Health Sciences Centre.

Participants underwent a clinical evaluation by one of the clinical investigators (ER, CF, or CS) for assessment of their concerns, symptoms, function, substance use, living circumstances, and severity of illness. They completed self-report questionnaires as described in Section 14.2.3. Based on the clinical evaluation combined with the assessment instruments, a primary (single) final hypothesized diagnosis was made prior to the participant being scheduled with a psychiatrist for definitive diagnostic assessment. Trauma related diagnoses [acute stress disorder and posttraumatic stress disorder (PTSD)] were identified and reported separately from the other anxiety disorders due to the differences in clinical needs for these conditions.

14.2.1 Participants

Youth, aged 16–26 years, were screened and excluded if they had a major medical problem, history of serious head injury, developmental delay, or the presence of an attention problem severe enough to have warranted psycho-stimulant medication since childhood. They were also excluded if they had previously been treated with medications for a total of 18 months in their lifetime, since this was exclusionary for entry into FEMAP. In addition, if the individual reported that his/her mood and/or anxiety symptoms only occurred after the onset of frequent use of a substance of abuse, then he/she was excluded and referred to an addiction service for youth in the community.

14.2.2 Demographics

Participants were administered a demographic questionnaire that included age, gender, and information about their living situation and parents. Youth were asked about their family income as well as parental marital status and mother and father's educational level. Unfortunately, many youth were not aware of their family's income. As a proxy for socioeconomic status, parental marital status and mother's educational level were used. Mother's educational status was considered a better proxy than father's since family income (and child academic achievement) better coincides with mother's education after divorce (14).

14.2.3 Questionnaires

The following well-validated questionnaires were administered to participants. The Beck Depression Inventory (BDI) (15) measures extent of depressive symptomatology; the SpielbergerState/Trait Anxiety Inventory-State (STAI) (16) measures extent of state anxiety symptomatology; the Emotion Regulation Questionnaire (ERQ) (17)

rates coping strategies related to the regulation of emotional states and is divided into two subscores – reappraisal and suppression; the Adult ADHD Self-Report Scale-version 1.1 (ASRS) (18) is a self-report measure of difficulties with attention; the NIDA Modified ASSIST (19) measures substance use habits and predicts risk of SUDs; the Sheehan Disability Scale (SDS) (20) includes three subscales that measure school/work, family life and social functional impairment; and the Youth Risk Behavior Survey (YRBS) (21) asks about a wide range of historical and recent risk behaviors common in youth populations.

Questionnaires representing trait coping styles were the ERQ and the ASRS. A total ERQ score was calculated as the sum of the Reappraisal subscale (considered to be an adaptive approach to emotion regulation) minus the sum of the Suppression subscale (thought to be a maladaptive approach to emotion regulation) (22). Since the ASRS was being used here as a general proxy for cognitive dysfunction in the spectrum of inattention, rather than as a predictor of the diagnosis of ADHD, a total score was derived by adding the total scores for part A and part B of the instrument.

Several items from the YRBS were analyzed as measures of early habits that we thought would be associated with subsequent substance use risk. These included the YRBS questions on age of first smoking of a cigarette, age of first alcoholic drink, age of first use of marijuana, and age of first sexual intercourse. The original items rank the answers from “never,” then “less than age 12” sequentially up to “17 or more years old.” For the linear regression analyses, these items were re-coded such that the answer “never” was higher than the highest age of first use, thereby creating a logically consistent ordinal scale. The YRBS questions about use of alcohol, tobacco and cannabis in the last 30 days were also hypothesized to be predictive of current cannabis use. The total scores for each substance from the ASSIST were used as risk scores for each of the substances of abuse, including cannabis, and the total ASSIST score provided a rating of overall risk for a SUD.

14.2.4 Analyses

Descriptive, frequency, regression and all other statistics were calculated using SPSS, version 20 (23). Data were explored for incorrect entries and these were corrected. Missing entries of data were treated by eliminating those cases from the analyses.

Backward selection multiple regression was chosen because this would provide the most parsimonious model to predict the dependent variable, given the identified independent variables which were all considered hypothetical predictors. A regression analysis was performed using the following variables to predict NIDA ASSIST total cannabis score: demographic variables of participants (age and gender); demographic variables of participants’ families (parental marital status, mother’s

educational level); trait variables related to coping and cognition (ERQ and ASRS); participants' early risk behaviors (age of first use of tobacco, alcohol and cannabis and first sexual intercourse); recent substance use (alcohol, cannabis and tobacco), and lastly, measures of psychiatric symptoms and functional impairment (BDI, STAI, total SDS score).

In addition, in order to better understand the contributions to functional impairment in this population and the extent of the association of cannabis use (and other variables) to functional impairment, a multiple regression using level of functional impairment (SDS score) as the dependent variable was conducted with the other variables listed above as predictor variables.

Skewness was evaluated for all variables used in the regression analyses and was found to be less than 1.5 for all. Although BDI and STAI were strongly correlated ($r = 0.64$, $p < 0.0005$), collinearity statistics for the group of variables did not indicate that the combination was problematic in the regression analyses (collinearity tolerances for all variables = 0.500).

14.3 Findings

Participants were 429 youth whose mean age was 19 (SD 2.7). These included 271 (63%) female and 158 (37%) male youth. The sample had well-educated mothers. The mean educational level was described as “some college or specialized education,” and the mode was “graduate from a college or university.” Fully 74% of respondents' mothers had at least some college or university education. A slim majority (54%) of participants came from families with married parents (including common-law married); while 46% came from families of separated, divorced or widowed parents.

14.3.1 Diagnostic characteristics

Of the participants, 325 (68%) received the primary hypothesized diagnosis of depression, anxiety or the combination of both, while 22 (4.5%) were thought to have a primary SUD, notwithstanding the pre-screen to exclude and refer such participants. Other diagnostic categories representing over 5% of the sample included: bipolar disorder (7.8%), trauma disorders (5.9%), and DSM-Axis IV disorders (9.4%). This latter category included participants who were evaluated to have problems related to life stressors (conflicts within the family, lack of stable housing or food, etc.), but did not have PTSD. For this category the clinical evaluator had to believe that these participants would not have sought help were it not for these stressors, and that the individual would be symptom free if these were corrected. Another 4.4% had a mixture of other Axis I diagnoses.

14.3.2 Coping styles

The mean difference score for the ERQ (Reappraisal minus Suppression) was 5.3 (SD 8.7, range -19–36). The ASRS mean total score was 8.5 (SD 4.4, range 0–18).

14.3.3 Participant risk behaviors

Among age of onset variables, the most frequently reported age of first smoking a cigarette in this sample was “never” (43% of sample). Only 38% of participants endorsed smoking a cigarette before the age of 17 (the remainder endorsed smoking for the first time at the age of 17 or older). In contrast, only 8% of subjects endorsed never having had a drink of alcohol and 78% reported drinking for the first time before the age of 17. Thirty percent (30%) endorsed never having tried cannabis and just over half, or 53%, reported using cannabis for the first time before the age of 17. Lastly, 33% of these youth reported never having had sexual intercourse, while 43% had sex for the first time before the age of 17.

The YRBS includes 30-day frequency of use of multiple substances, including cigarettes, alcohol and cannabis. Sixty-four percent (64%) of our sample endorsed using no cigarettes in the past 30 days. In contrast, just under one third (31.5%) of participants reported no alcoholic drinks in the last 30 days, while 37.5% endorsed alcohol use on more than 3 days in the past 30 (the remainder used alcohol between 1 and 3 days in the last 30). Lastly, 62% of our sample reported no cannabis use in the last 30 days, and 21% reported using cannabis 10 or more times in the last 30 days (the remainder used cannabis one to nine times). As expected, there was a high correlation between 30-day cannabis use frequency and ASSIST total cannabis score ($r = 0.86$, $p < 0.0005$). Therefore, 30-day cannabis use frequency was not used in the regression analysis but 30-day tobacco and alcohol use frequencies were.

14.3.4 Psychiatric and SUD symptoms

The symptoms score means, standard deviations (SD) and ranges were as follows for the various symptom questionnaires. BDI mean = 31 (SD = 11.6, range 0–59), which was in the severe range of depressive symptomatology; STAI mean = 56 (SD = 12.0, range 20–80), which was at the high end of the moderate range of anxiety; SDS mean = 20 (SD = 6.3, range 1–30); ASSIST total cannabis mean = 8 (SD = 10.9, range 0–39). In addition, the ASSIST defines score ranges to identify low, moderate and high substance use risk based on questionnaire total score. In this sample, 50.3% were at low, 32.6% were at moderate and 17.0% were at high risk for SUDs.

Use of other substances was also evaluated by the ASSIST, including cocaine, stimulants, methamphetamine, inhalants, sedatives, hallucinogens, street opioids,

prescription opioids, and “other” drugs. In this sample, rates of use of these drugs were low. The most commonly used illicit drugs after cannabis were sedatives, (16.3% of sample had non-zero total scores), and hallucinogens (16.1% had non-zero total scores). For all other substances less than 10% of participants admitted to having used each of them.

14.3.5 Multiple regression

Using the backward selection method, a significant model emerged as associated with ASSIST total cannabis score [$F(7, 421) = 37.943, p < 0.0005, \text{Adjusted } R^2 = 0.377$]. Significant variables are shown in Table 14.1.

Additionally, a significant model emerged as associated with total level of functional impairment per the SDS score [$F(5, 423) = 42.442, p < 0.0005; \text{Adjusted } R^2 = 0.326$]. Significant predictor variables are shown in Table 14.2.

Table 14.1: Multiple regression (backward selection) predicting NIDA modified ASSIST total cannabis score*

Predictor variable	Adjusted beta	Significance (p)	95% Confidence interval for B	
			Lower bound	Upper bound
Gender (male = 1, female = 2)	-0.195	<0.0005	-6.184	-2.664
Age first use marijuana	-0.263	<0.0005	-2.961	-1.404
30-day cigarette use per day	0.278	<0.0005	1.241	2.399
Sheehan Disability Scale score	0.137	<0.001	0.104	0.370

* Independent variables that were not predictive in this model included: age; mother’s educational level; parental marital status; ADHD Self-Report Scale; Emotion Regulation Questionnaire; age of first tobacco or alcohol use or first sexual intercourse; 30-day alcohol use; State Trait/State Anxiety Inventory (state) score; and Beck Depression Inventory score.

Table 14.2: Multiple regression (backward selection) predicting total Sheehan Disability Scale score*

Predictor variable	Adjusted beta	Significance (p)	95% Confidence interval for B	
			Lower bound	Upper bound
ADHD Self-Rating Scale score	0.097	0.029	0.014	0.264
Beck Depression Inventory score	0.494	<0.0005	0.223	0.316
NIDA modified ASSIST total cannabis score	0.167	<0.0005	0.045	0.148

* Independent variables that were not predictive in this model included: age; gender; mother’s educational level; parental marital status; Emotion Regulation Questionnaire score; age of first cigarette, alcohol or marijuana use; age of first sexual intercourse; 30-day alcohol use; 30-day cigarette use; and State Trait/State Anxiety Inventory (state) score.

14.4 Discussion

In this chapter we investigated the risk levels of SUDs, cannabis use, and functional impairment in a sample population of 429 youth aged 16–26 who presented for evaluation and treatment of mood and/or anxiety problems, and who were screened to exclude youth with primary SUDs. In spite of this screening, a small percentage (4.5%) was thought to have had a primary SUD after clinical assessment. A much larger percentage of the youth, approximately half, were found to be at either moderate or high risk for a SUD.

Our results showed that predictors of heavy cannabis use included being male, early first use of marijuana, high 30-day use of cigarettes, and high levels of functional impairment. Contrary to what might be expected, lower socioeconomic status, using the proxies of maternal educational level and parental marital status, was not predictive in this model. However, it should be noted that the socioeconomic status of this population appeared to be higher than average compared with the general population.

The coping styles identified by ASRS and ERQ scores were also not predictive. This sample excluded subjects with ADHD diagnosed and treated in childhood, so participants were not representative of the full range of ASRS scores in a general clinical population. This may account for an absence of predictive significance for this variable, although ASRS score was predictive of functional impairment in the regression analysis with the same participants.

Anxiety or depression scores were not predictive of total cannabis score, which was also counter to our predictions, although total depression score (but not anxiety score) did predict overall functional impairment.

Interestingly, age of first cigarette and alcohol use were not predictors of cannabis total score, but age of first cannabis use was, as would be expected. Even though an early onset of smoking tobacco did not predict total cannabis score, 30-day tobacco use did. While the rate of tobacco use found here was quite low compared with that of cannabis, our cohort nevertheless reported almost twice the overall rate of cigarette use of high school students in North America (12, 13). Previous reports have found higher rates of tobacco use in individuals with mental health symptoms, including non-psychotic symptoms (24–26). Our findings indicated that only recent tobacco use was associated with higher scores of total cannabis use.

Our results lead to the conclusion that total cannabis use was best predicted by being male, younger age of onset of cannabis use (but not the other risk behaviors measured), high frequency of recent cigarette (but not alcohol) use, and total degree of functional impairment.

This last predictor, functional impairment, was perhaps our most clinically relevant variable. Investigated as the dependent variable as well, total level of functional impairment in our sample was predicted by ASRS (measuring cognitive coping style), BDI score (measuring current depressive symptom severity), and the total cannabis

score, but was not predicted by demographic variables, age of onset of risk behaviors, emotion regulation style, state anxiety, or recent substance use. These results confirmed our clinical impression that greater cannabis use was associated with a higher degree of dysfunction in our youth seeking help for mood and/or anxiety symptoms. We believe this to be the first report that investigated cannabis use and functional impairment in youth with mood and/or anxiety disorders. Since cannabis is the most commonly used illicit substance by youth in North America (12, 13), this association is clinically important.

There has been a dramatic decrease in the use of tobacco products by youth since 1997, while rates of cannabis use have fluctuated around a largely unchanged rate of use (12, 13). The cigarette smoking decreases may be related to public health campaigns educating about the negative health effects of tobacco use (27). No similar public health campaign exists yet aimed at reducing cannabis use in youth.

The limitation of this study is the unknown representativeness of this clinical sample to youth with mood and/or anxiety disorders in general. Nonetheless, this research has suggested that roughly half of youth seeking help for mood and/or anxiety disorders screened to exclude those with a primary SUD are, in fact, at risk for a SUD. It also showed that there was an association between cannabis use and functional impairment. Those at risk for cannabis use were more likely to be male, to have engaged in marijuana use at an earlier age, to have higher recent cigarette use, and to endorse greater functional impairment. This indicates a strong need for substance use specialists for the clinical youth population with mood and/or anxiety complaints even when they do not appear to have a primary SUD. Including such services in primary care and specialized clinics treating youth with mental health concerns appears to be important for ensuring the best care to reduce symptom severity and negative outcomes associated with co-occurring mental illness and SUDs, as well as to improve treatment responses.

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Section VI: **Veterans' issues**

15 Military sexual trauma as a determinant in the development of mental and physical illness in male and female veterans

Betsy S. O'Brien and Leo Sher

Military sexual trauma (MST) is defined as sexual harassment and or sexual assault experienced by a military service member. It is much more widespread and common than reported. It is associated with pre-combat traumatic experiences and pathologic sequelae including mental and medical illness. Methods: An electronic search of the major behavioral science databases was conducted to retrieve studies detailing the social, epidemiological, and clinical characteristics of MST and its relationship to psychiatric and medical illness. Results: Studies indicate that military sexual trauma is related to an increase in psychiatric pathology including PTSD, substance abuse and dependence, depression, anxiety, eating disorders, and suicidal behavior. MST is also related to an increase in medical illness, primarily pain related symptoms involving multiple organ systems including gastrointestinal, neurological, genitourinary, and musculoskeletal. Conclusion: MST is associated with an increased prevalence of mental and physical illness. Although there are some gender differences in the reported rates of MST and there may be some variables, such as prior traumatic experiences, that may make an individual more vulnerable to the psychiatric and medical sequelae of MST, it is clear that MST is a major health care issue that affects both sexes and warrants further attention and an increase in clinical resources devoted to it. Some preventive measures for decreasing the prevalence of MST may include increasing education and legal prosecution of perpetrators in the military, and increasing access to mental health services for individuals who have suffered from MST.

15.1 Introduction

The Department of Veterans Affairs has defined Military Sexual Trauma (MST) as sexual harassment and or sexual assault experienced by a military service member without regard of the location of service, gender of the victim, or relationship of the victim to the perpetrator (1). In 1992, there was a congressional mandate for the Department of Veterans Affairs to treat veterans for symptoms related to MST (2). The data on the prevalence of MST contains some variability, depending if the studies only include actual or threatened sexual assault or more broadly include offensive sexual behavior or unwanted sexual attention. For example, Allard et al (2) cited a prevalence estimate of between 22–45% as based on prevalence studies which primarily include actual or threatened sexual assault. In 2006, the Department of Defense (DOD) conducted a study, which also estimated prevalence of MST and cited prevalence numbers for different types of MST. Specifically the DOD estimated that

52% of women and 29% of men reported offensive sexual behavior, 31% of women and 7% of men reported receiving unwanted sexual attention, 9% of women and 3% of men reported sexually coercive behavior, and 6.8% of women and 1.8% of men reported being sexually assaulted (1). Data from OEF/OIF (Operation Iraqi Freedom, OIF and Operation Enduring Freedom OEF, Afghanistan) veterans suggests that 15.1% of women and 0.7% of men reported MST when screened (3).

Individuals that are most vulnerable for MST are most likely to be women between age of 30 and 49 years, White, highly educated, served in the reserves more than 5 years, and more likely to have a service-related disability (4). Alcohol abuse is another risk factor that increases instances of MST and an estimated 50% of sexual assaults in the military have alcohol involvement (5). As women become an increasing part of the total veteran population, prevalence of female veterans estimated at 15%, when including the wars in Iraq (Operation Iraqi Freedom, OIF) and Afghanistan (Operation Enduring Freedom OEF) (3), MST becomes a larger health issue affecting the military as well as the veteran population.

15.1.1 Recognition of MST

The diagnosis of PTSD, included in the DSMIII and in the manual PTSD, was seen as the result of certain gender specific stressors mainly combat for men and rape and sexual trauma for women (6). Sources have suggested that seeing certain stressors as gender specific, such as rape for women and combat for men, has perhaps led to a decrease in reporting MST and thus artificially lowered the MST prevalence rates in male veterans (6). Initially in the first decade of DoD research on MST in servicemen, the reported rates were less than 1% (6). Then during the 1990s there was an increase in reported rates of men's MST to 2–9% (6). Now reported rates of men's MST vary widely across studies in the DoD from 0.02% to 12% (6). Sources have also looked at non-response rates, which ranged from 3–92%, and have extrapolated that 66% of men's sexual assault incidents are not formally reported and that only 10% of sexual assaults on men at the service academies are thought to be reported (6).

The question arises as to what causes this under-recognition of MST especially in the male veteran population. Some studies have suggested that those who do not report want to avoid thinking or talking about an assault and do not want to disclose the event, whereas other sources have suggested that the military and government have created certain administrative barriers to reporting MST including length of questionnaires, substantial number of surveys to fill out, and fostering a perception that the surveys will not change policy (6). The military philosophy as well with its emphasis upon the need for cohesion, discipline, loyalty, and collectivism may create an environment that discourages reporting of sexual assault and the feeling that the victims will be attacked verbally and even physically for reporting (5, 6). Studies quote common reasons for not reporting MST to be that victim feels embarrassed, fearful of

reprisal through evaluations, belief that the incident was not important enough to warrant reporting, and fear nothing will be done (6). An element of guilt may also play a role in not reporting the crime as male victims of MST may interpret reporting to be a threat to their manhood (6). Studies have also shown that MST affects military careers as a substantial portion transfer or leave the services as a result of their experiences (7), which may decrease the likelihood of reporting the incident.

15.1.2 Civilian traumatic experiences and MST

Military personnel in general report higher rates of trauma before, during, and after their military involvement than civilian population (2). Allard and colleagues (2) suggested that the prevalence of rape among female veterans (49%) was significantly higher than among civilians (22%). Kelly and colleagues (8) reported that of the 135 female participants that stated MST in their study, 95.4% also reported at least one trauma in addition to the MST, the most common being sexual abuse as adult civilians (77%) and then sexual abuse as children (53%) (8).

Being in the military does not make women less vulnerable to intimate partner violence. Studies have shown that in a sample of females enlisted in the army married to civilian spouses, the sample of women were almost four times more likely to be victims of unilateral violence from their non-military spouses than perpetrators of unilateral violence (4). The women were also three times more likely to be victims of severe violence from their partners, which is similar to non-military studies of intimate partner violence (4).

15.1.3 Literature search

An electronic search of the major behavioral science databases (PUBMED, PSYCINFO, MEDLINE) between the years 1990–2012 was conducted to retrieve studies detailing the social, epidemiological, and clinical characteristics of Military sexual trauma and its relationship to psychiatric and medical illness. Search items included “military sexual trauma,” “childhood trauma,” “veterans,” “post-traumatic stress disorder,” “depression,” “female veterans,” “male veterans,” and “medical illness.” Additional references were incorporated from the bibliographies of the retrieved articles.

15.2 Findings

Sources have shown that since returning from Iraq 15% of service members meet criteria for major depression, generalized anxiety disorder, or PTSD and 11% from Afghanistan (3). The mental health consequences of MST include PTSD, alcohol abuse, depression,

somatization disorders, suicidality, and impulsive behavior (3, 4, 7, 9–12). MST has also been correlated with difficulty with psychosocial readjustment to civilian life, particularly in areas involving intimacy (13).

Studies have also associated MST with suicidality in both genders (4, 12). Interpersonal trauma and sexual assault during military service was associated with suicide attempts in both military men and women (4).

15.2.1 MST and psychiatric illness in females

The most prevalent trauma-related mental health problem is PTSD with the lifetime prevalence of PTSD among female veterans attending VA primary care clinics being 27% (7). Women veterans who suffered from MST are nine times more likely to develop PTSD than women without a history of sexual assault (4). Studies have also identified that MST specifically, more than other trauma, is a stronger predictor of PTSD (14–16). In one study, 60% of women veterans who suffered from MST were diagnosed with PTSD using the DSM-IV criteria versus 40% of women veterans who suffered from other traumas both pre-service, during service, and post-service including sexual and physical assault, witnessing violence, combat trauma, illness, accidents, traumatic deaths, and natural disasters (14). Suris and colleagues (16) also showed that MST specifically is a stronger predictor of PTSD than other sexual trauma. They found that female veterans were nine times more likely to have PTSD if they had a history of military sexual trauma versus seven times more likely if they had a history of child sexual abuse versus five times more likely if they had civilian sexual assault histories in comparison with female veterans who do not report a history of sexual assault (16).

MST is also correlated with other Axis I diagnoses, mental health symptoms, and use of prescription medication for mental health symptoms (17). For women who reported military-related sexual assault, screening prevalence for current depression was three times higher and for current alcohol abuse three times higher than for women veterans not reporting MST (11). Furthermore, some studies have suggested that the majority of female veterans with PTSD will have comorbid psychiatric illness, with some research supporting a link between PTSD and substance abuse (7). With respect to eating disorders and impulsive behavior, sources have suggested a prevalence of eating disorders of about 25% in female veterans who have suffered from MST (10). Studies have shown that MST itself has been linked to eating disorders and substance use (9). Other studies have identified four major coping strategies for females with post-deployment stress including coping with the aftermath of MST. These coping strategies include disordered eating behavior, substance abuse, and impulsive behavior including bingeing and purging, compulsive spending, over-exercising, and prescription drug abuse (3).

15.2.2 MST and psychiatric illness in males

Similar to female veterans, male veterans who experienced sexual harassment and assault have greater incidence of PTSD, depression, and somatization disorders than male veterans who had not experienced sexual harassment (4). Studies have suggested that perhaps due to an increase stigma attached to MST in male veterans and a decrease in reporting of MST amongst male veterans, there may be greater levels of psychological sequel including PTSD and other psychiatric symptoms as well as poorer physical health (2). Studies have shown that sexual harassment of men in the military has shown a stronger association with psychological problems including more persistent sexual abuse trauma symptoms, more persistent sexual problems, more emotional problems, and a larger decrease in work productivity than women (6, 18). Some studies have also shown that psychological problems also appear to be more persistent and treatment resistant after MST in men than in women (6).

15.2.3 MST and medical illness

Associations between stress reaction and physical illness are seen throughout medical systems including cardiovascular, respiratory, GI, cancer, and chronic pain problems in both females and males. Studies have shown that war zone stressor-related trauma was associated with increased disordered functioning in arterial, gastrointestinal, and musculoskeletal systems in female and male veterans (19). In female and male veterans, MST is associated with physical health problems, primarily pain related and affecting multiple organ systems including genitourinary, musculoskeletal, neurological, and gastrointestinal (4). Individual physical symptoms include back pain, headaches, GI symptoms, and chronic fatigue (4). MST has also been associated with an increase in health risk factors including obesity, smoking, and sedentary lifestyles (4, 18). MST is also associated with chronic medical comorbidities including liver disease and pulmonary disease (4). MST has also been associated with sexual dysfunction in both female and male veterans (2).

15.2.4 MST and medical illness in females

Many studies restricted the study population to female veterans as MST is more common in the female veteran population as highlighted above. These studies found that MST in female veterans was correlated with an increase in chronic medical problems (17) as well as current symptoms across almost every organ system assessed including reproductive/gynecological, urological, neurological/rheumatological, gastrointestinal, pulmonary, cardiovascular, and other symptoms including chronic fatigue (20). Women veterans who reported sexual assault while in the military were

more likely to report a heart attack within the previous 12 months than women who had not reported sexual assault while in the military (9). A reported history of MST was also associated with an increase in cardiac risk factors including obesity, smoking problem alcohol use, and sedentary lifestyle (9). For female veterans, metabolic comorbidities including hypothyroidism also associated with MST (4). Women also reported more frequent symptoms of pelvic pain, vaginal bleeding/discharge, painful intercourse, rectal bleeding, bladder infections, and painful urination compared to those not sexually assaulted (4). Female veterans who were victims of MST also report sexual dysfunction including decreased sexual satisfaction as well as fear, disdain, or avoidance of sexual intimacy, and difficulty with arousal and desire (2). MST was also associated with poorer reproductive outcomes in women including infertility and lost pregnancies (20) as well as hysterectomy before the age 40 years (9).

15.3 Discussion

Sources have suggested that psychiatric sequela may mediate the relationship between MST and medical illness, especially PTSD (14). Sources have shown that post-traumatic stress symptomatology (PSS) mediates the relationship between violence and physical health symptoms (19). Some studies have suggested that there are gender differences in the relationship between MST and physical health symptoms and that PSS mediates the relationship between MST and perceived physical health in men but not in women (19).

Smith and colleagues (19) separated sexual harassment from sexual assault and found that sexual harassment was not a significant predictor of post-traumatic stress symptomatology when warfare stressors were not included, thus indicating that warfare stressors may actually be the mediator between sexual harassment and physical illness including gastrointestinal and neurological symptoms in male veterans who suffered from sexual harassment (19). However, sexual assault was a significant predictor of post-traumatic stress symptomatology (PSS) even when warfare stressors were controlled for (18). Furthermore, for veterans who suffered from sexual assault, PSS mediated the relationship between sexual assault and health symptoms including gastrointestinal (primarily abdominal pain), genitourinary (primarily sexual discomfort or difficulties), musculoskeletal (primarily muscle or joint pain), and neurological (primarily headaches) (19).

15.3.1 Pre-military abuse as a predictor of PTSD and mediator between MST and mental and physical illness

Not all veterans who suffer from military trauma, whether it be MST or combat-related trauma, will go on to develop PTSD, but it does appear that veterans are more predisposed to PTSD symptomatology than the civilian population. As mentioned above,

military personnel have a higher prevalence of trauma before, during and after their military involvement (2). Studies have shown that female veterans in Desert Storm who describe pre-service abuse reported greater PTSD symptomatology than those denying pre-combat abuse (21). In a study with 2,392 male soldiers returning from Iraq, those that suffered from childhood trauma were more likely to have positive screenings for both PTSD and Depression (22). The same trend was seen with Vietnam veterans in which Vietnam Veterans with PTSD had higher rates of childhood physical abuse than Vietnam veterans without PTSD and veterans with PTSD overall had higher total traumatic events before joining the military than patients without PTSD (23). It is possible that this may apply to MST and that those who suffer from pre-MST abuse may be more vulnerable to PTSD symptomatology than those who deny pre-MST abuse.

If PTSD is a mediator between trauma and the development of physical illness and the presence of multiple traumas is a predictor of PTSD, we propose that veterans who suffer from multiple traumas, with MST being one of those traumas, are the veterans who are more vulnerable to developing physical illness in the aftermath of MST. Perhaps it is both the prevalence of multiple traumas and the development of PTSD that mediates the relationship between trauma and the development of both mental and physical illness. Previous studies have supported that multiple traumatic events increases vulnerability for medical illness. In the Adverse Child Experience Study (ACE Study 1998), children who have suffered from multiple adverse childhood (defined as experiencing 4 or more categories of childhood exposure) had a 4- to 12-fold increased prevalence of multiple poor mental and physical health outcomes including alcoholism, drug abuse, depression, suicide attempt, smoking, sexual promiscuity and sexual transmitted diseases, obesity, and physical inactivity as well as increased risk for medical illness including ischemic heart disease, cancer, chronic lung disease, skeletal fractures, and liver disease (24). We suggest that there may be a similar outcome with the veteran population with those veterans who suffered from MST as well as multiple other adverse experiences pre-combat have an increased risk of mental and physical illnesses.

15.3.2 Prevention and treatment

Education of military personnel about MST as to increase awareness and reporting is necessary. Awareness and discussion of MST is often avoided especially if the perpetrator is a coworker or a superior officer as it disrupts the focus of military experience including closeness, dependence, cohesion, and leadership which in the military are often necessary for survival especially in combat (2). The reporting system in the military also contributes to underreporting of MST as well as decreased law enforcement against perpetrators of MST (5). The reporting system in the military is a two-tiered system (5). The first tier of reporting is where the victim anonymously

files a restricted report of the assault and can receive medical care and counseling, but does not prosecute the perpetrator (5). The second tier of reporting the victim also prosecutes the perpetrator, but no longer remains anonymous (5). Although this two-tiered reporting system may increase the number of victims who seek treatment, it does not bring justice to the perpetrator and may do little to prevent the continuation or even escalation of MST in the military (5). Thus in order to prevent the perpetuation of MST it becomes important to not only educate military personnel but also to remove barriers to reporting and prosecuting perpetrators of MST.

In the aftermath of MST, treatment and access to treatment becomes essential. Increasing access to supports in the aftermath of trauma while veterans are still in active duty may be necessary to facilitate recovery, but difficult in the military where deployment means one is cut off from primary support systems (2). That being said, barriers to treatment continue to exist after deployment. Access to treatment is important. Some studies where women veterans were interviewed described that female veterans did not feel comfortable seeking VA services as they felt that WWII, Korean, or Vietnam veterans should be entitled to VA services before them (3). For women who suffered from MST there is also a fear of utilizing services where they may encounter the same type of individuals who perpetrated the sexual trauma (3). Childcare also may be a barrier for women seeking services (3). There also needs to be an increased availability of mental health treatment specific for sexual assault related psychopathology including Prolonged Exposure (PE) and Cognitive Processing Therapy (CPT) as well as some other less empirically supported modalities (Stress Inoculation Training and Eye Movement Desensitization and Reprocessing) (1).

In conclusion, MST is a clinically significant issue that deserves recognition and discussion for both men and women. Although there are some gender differences in the reported rates of MST, physical and psychological sequela, it is clearly a major health care issue that affects both sexes and warrants further attention and an increase in clinical resources devoted to it.

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16 Educating medical professionals about suicide prevention among military veterans

Debora Ganz and Leo Sher

The aim of this chapter was to discuss the results of a review into the literature related to suicide in military veteran populations. Suicide in veteran populations has been increasing in recent years, and continues to be a medical and social problem across the globe. For medical health professionals, knowledge of the risk factors for suicide, careful assessment, and appropriate interventions are key to suicide prevention. This review seeks to better understand the risk factors present in veteran suicide and how to best educate medical professionals in suicide prevention. Key suicide risk factors found in veteran populations include post-traumatic stress disorder, major depressive disorder, physical injuries, substance use disorders, traumatic brain injury, combat related guilt, access to firearms, and insufficient social support. Some psychosocial difficulties are unique to veteran populations, and medical professionals should be culturally sensitive to these factors. Psychosocial changes upon discharge from active duty, as well as stigma against mental health disorders and treatment, should also be considered and assessed. Since general practitioners may be the first line of defense for these veterans, they should be educated in risk factors for veteran suicide and proper assessment techniques. Any suicide risk in a veteran population should be taken very seriously, and responded to appropriately.

16.1 Introduction

In 2006, suicide was reported to be the 11th leading cause of death in the United States (US), with more than 32,000 individuals killing themselves each year (1). A cross-national study involving nine countries and over 40,000 persons found the rates/100 for suicide ideation ranged from 2.09 (Beirut) to 18.51 (Christchurch, New Zealand), with lifetime prevalence rates/100 for suicide attempts ranging from 0.72 (Beirut) to 5.93 (Puerto Rico) (2).

Suicidality exists along a continuum ranging from suicidal ideation to completed suicide. For the purposes of this article, we will focus on the research concerning suicidal ideation, suicide attempts and completed suicides in international military personnel.

Suicidal behavior is both a medical and social problem throughout the world. In the US in 2000, the average cost per case for a fatal self-inflicted injury (suicide) was \$2,596 in medical costs and \$1.0 million in lost productivity (3). Suicidality is also commonly associated a variety of medical and psychosocial factors, including depression, alcohol and drug abuse, traumatic brain injury (TBI), suicide contagion, combat-related guilt and decreased social support (4). A necessary step in reducing these costs is educating medical professionals to recognize suicide risk factors and enact appropriate preventative measures.

16.2 Prevalence of suicidal behavior

Suicide rates in US military typically fluctuate between 9.0 and 15.0 per 100,000 persons per year (5). However, different studies across countries and over time have found disparate results, with some indicating that suicide rates are higher in military than civilian populations, while others have found no significant differences in suicide rates (6–14). According to some findings, suicide attempts in Canada as well as completed suicides in US tend to be lower in the military than in comparable civilian populations (7, 8). Other statistics indicate that from 1980–2004, the crude rate of US active duty military completed suicides averaged at 12.4 per 100,000 persons per year, while the civilian suicide rate averaged at 12.5 per 100,000 persons per year (5, 9). Increases in the rates of suicidality in the Romanian, Ukrainian and Norwegian militaries have been observed in recent years (7). Possible reasons for these disparate results, with suicide rates among veterans sometimes being lower than in the general population, may be a result of screening procedures for mental health problems prior to enlistment, suicide prevention programs for enlisted soldiers or other protective factors within the military (6, 7).

According to a recent CBS news study, veterans committed suicide at the rate of 18.7–20.8 per 100,000, compared to the normative American population, who did so at the rate of 8.9 per 100,000 (10). Over 20% of Operations Enduring Freedom and Iraqi Freedom (OEF-OIF) veterans reported recent suicidal ideation (in the past 3 months), compared to less than 3% in the general population (11, 12). Some studies suggest that male Veterans are at twice the risk of suicide than comparable men in the general population, and female veterans are thought to be at a three times higher risk of suicide than comparable female populations (13). Veteran's aged 20 through 24 who served during the war on terror had the highest suicide rate of all veterans (22.9–31.9 per 100,000), estimated between two and four times higher than the suicide rate for civilians in the same age group (8.3 per 100,000) (10). However, other studies maintain that suicide risk of veterans overall (specifically gulf war veterans) was not significantly different from that of the general population (6). While risk factors for suicidality differ across nationality based on specific missions, social situations and recruitment policies; it seems to be true that increased suicide rates are present in veteran populations and increasingly prevalent in armies that recruit more adolescents (i.e., Israel) due to elevated rates of adjustment disorder in that age group (6, 7, 10, 14).

16.3 Risk factors for veteran suicide

There are many possible reasons for the significant suicide rates among war veterans; many of which are distinct from civilian suicide risk factors. While post-traumatic stress disorder (PTSD) may be the most widely researched, other factors that contribute to suicide in military personnel include major depressive disorder (MDD),

physical injuries, substance use disorders, TBI, combat guilt, survivor guilt, access to and familiarity with firearms, and psychosocial difficulties (4, 15, 16). In 2008, a US congressional report concluded that the main suicide risk factors for veterans were: combat exposure, PTSD, mental health problems, TBI, poor social support and access to lethal means (16).

Psychopathology is typically associated with an increased risk for suicide attempts, and this is true of combat veterans as well. Combat veterans with psychiatric symptoms are more likely to make a suicide attempt than combat veterans without psychiatric symptoms (15). Two studies involving more than 450 veterans from the UK indicated that personnel with mental health problems during service were likely to present with depression (48%) and stress (28%) after discharge (17, 18). Specific cognitions that may indicate increased suicidal ideation in military personnel are those related to combat guilt and survivor guilt (19). These specific cognitions were also found to be associated with combat related PTSD (19), and may be a moderating factor between PTSD and suicidality in veteran populations.

Some culturally specific factors that may contribute to suicidality include the aggressive nature of the army, the demands of a military lifestyle, increased access to and knowledge of firearms and possibility for suicide contagion among fellow soldiers (7). Decreased social support has also repetitively been found as a risk factor for suicide in veteran and civilian populations (4, 6, 7, 16). Some specific suicide risk factors associated with negative life events that have been documented in military populations include wanting a change (in military position), anger at an external entity (e.g., their general), conflict in a romantic relationship and past suicide attempts (7, 20).

Recent veterans are at an elevated suicide risk, possibly because protective structures and cognitions that existed during active duty may no longer be in place (21). While a military lifestyle may be a protective factor for many, the transition from military life to civilian life may serve to compound suicide risk by resulting in social exclusion, homelessness, alcohol misuse, unemployment, and/or poor mental health (6).

Since military and veteran lifestyles have unique psychosocial and economic challenges, training opportunities that incorporate role-play may help to prepare health care personnel to best treat veteran populations.

The interpersonal-psychological theory of suicide (20) is also able to account for some of the increased risk of completed suicide among military veterans (22). According to the interpersonal-psychological theory of suicide; the suicidal process is related to feelings of thwarted belongingness, perceived burdensomeness, and an acquired capability to overcome the pain associated with suicide (20). Within the realm of acquired capability to enact self harm, one of the factors contributing to completed suicides is access to lethal means (20). In fact, firearms account for nearly 50% of all US suicides (23). Due to military veterans increased access to and experience using firearms, an increase in their suicide risk has been found (16).

Within this theory, another important risk factor for completed suicide is that of increased pain tolerance. Such increased tolerance is often seen in war veterans due to

the fact that “repeated experiences with violence, even when directed towards others, may result in habituation and the acquisition of the capacity for self harm” (20, 22). A study done on nearly 45,000 wounded Vietnam veterans bolstered this hypothesis by finding an association between wounding and subsequent suicide risk (24). Similarly, research suggests that combat exposure, PTSD and TBI are each thought to increase the chance of suicide attempts; all of which are related to exposure to physical pain (16).

Research has found that TBI survivors are at increased risk for suicidal ideation, suicide attempts and completed suicides (25). TBI is also one of the leading injuries faced by US soldiers who served in Iraq and Afghanistan in recent years, thereby furthering the need for current suicide interventions for veterans. Medical professionals should specifically be familiar with the biological interactions between TBI and suicide, and the relevant medications.

16.4 Suicide prevention and assessment

A recent survey study in the United Kingdom (UK) found that about 50% of veterans with self-reported mental health problems sought help from their general health practitioner (GP) (17). In the US, a systematic review published in the *Journal of the American Medical Association* found that training primary care physicians in the recognition and screening of depression might be one of the most effective ways to prevent suicide (26). These findings highlight the need for medical health professionals to be educated about suicide risk factors in veteran populations.

Medical health professionals should take any suicidal ideation present in veteran patient populations very seriously. They should also be aware that they may be the first, (and possibly only,) means of suicide prevention for these individuals. They should be especially concerned with a veteran who also presents as depressed, traumatized, guilty or hopeless. It is important to ask about social support and access to lethal means (especially firearms or pills) and be prepared to follow-up with appropriate preventative measures.

Perhaps one reason for insufficient suicide prevention in veteran populations is a result of limited education of medical professionals on recognizing veterans in distress. There should be lessons on these factors in medical education and testing, role play of suicide related histories and cognitions, and increased distribution of what we know about suicide in veteran populations; via pamphlets, lectures and continual education courses.

Distribution of pragmatic and effective screening material is also imperative. A recent 3 question PTSD screen has been found to have a sensitivity of 78% and specificity of 87% in primary care settings (27). Such screening instruments may be a good place for GPs to start. However, since many veterans with suicide risk factors may not in fact be suicidal, a more comprehensive assessment may be necessary, with recognition that the more risk factors that are present, the higher the suicide risk (28).

Reduction in stigma may also be an important factor for medical professionals to consider when asking about suicidality, as a recent review found that US airmen avoided seeking professional help due to the stigma associated with mental health disorders and treatment (29).

16.5 Veteran suicidal ideation follow-up care and treatment

What should health care professionals do if they identify a veteran with suicidal ideation, suicidal intent, or a suicide plan? Rehabilitation options include inpatient and outpatient programs, hospitalization, and treatment of the related psychiatric, neurological and/or medical conditions.

If a veteran is determined to be in immediate risk of self-harm, hospitalization should be encouraged and likely mandated. This may be indicated if a veteran presents with many risk factors and an intent to die, expresses a great deal of hopelessness and has access to lethal means. If a veteran is determined to be at high risk with many risk factors, but not immediate risk, inpatient and/or day programs may be more appropriate. If a veteran presents with mild to moderate suicide risk, outpatient programs including cognitive behavioral therapy, family therapy and/or medication may be more appropriate (20, 22). Such an individual may have a few risk factors and occasional or passive thoughts about suicide, but deny access to means or any active suicidal intent.

For any level of suicide risk, a suicide prevention plan should be considered, with the individual agreeing to contact either health care or a responsible family member if they get the urge to commit suicide in the future (22). For lower levels of suicide risk, providing the patient with a suicide hotline or mental health contact is encouraged. This may be specifically helpful for veterans presenting with indications of depression and/or PTSD.

Regardless of the precise prevalence of suicide risk in each country, all veterans (if not all patients) should be asked about feelings of depression and suicidality (26). For all levels of suicide risk, proper consideration and appropriate safety planning should be effected with the patient. For any of these preventative measures to be effected, sufficient education of medical personnel is a necessary first step.

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Section VII: **Public health, cultural, and legal issues**

17 Does the physician density affect suicide rates among adolescents and young adults?

Leo Sher

Higher physician-per-population ratio may improve access to medical care, decrease waiting times, increase the opportunity for contact between the patient and physician and has been associated with earlier stage of diagnosis and better prognosis in patients with some medical conditions. It appears that an increase in the physician density generally improves the quality of health care and should prevent suicides. However, several research reports suggest that of those people who committed suicide, many saw a physician shortly before their suicide completion. Besides, studies show that many physicians do not have adequate training in suicide evaluation techniques and treatment approaches to suicidal patients, especially young people. Therefore, we hypothesized that the physician density does not affect suicide rates among adolescents and young adults. Methods: Correlations were computed to examine relationships between suicide rates in 15–24-year-old and 25–34-year-old males and females and the physician density in European countries. Countries were also divided into two groups, according to the median split of the physician density. Suicide rates among 15–24-year-old and 25–34-year-old males and females in these two groups were compared using the t-test. Results: We found no relationships between suicide rates and the physician density. Conclusion: The results of our study suggest that either physicians do not take an appropriate care of suicidal patients, or suicide is not preventable, or both. The results of this study should be treated with caution because many confounding variables are not taken into account.

17.1 Introduction

Physician density is the number of physicians, including generalist and specialist medical practitioners, per 1,000 of the population (1). It has been suggested that higher physician-per-population ratio may improve access, decrease waiting times and increase the opportunity for contact between the patient and physician (2). An increase in physician density tends to lead to physician-induced demand (3). The increase of health care consumption can be intuitively considered a “normal” effect of increased care availability in regions with a previous “low” physician density and unmet health needs.

The relationship between physician supply and the quality of care has recently sparked a debate about the required physician workforce in the US. The Association of American Medical Colleges called for an increase of medical school admissions by 30% annually to meet the increasing demand for health care of an aging population (4).

A study in Canada suggested that an additional family physician per 10,000 population has a statistically significant impact in the order of 2–4% on self-reported general health status, as well as, other quality of care outcomes (5). An analysis of the relationship between physician density and infant mortality, internationally and within the US has shown a strong relationship across countries but no relationship within the US, where physician density is on a relatively high level (6). One study found a negative correlation between metropolitan area level physician density and total mortality rates (7). The correlation becomes insignificant, however, when socioeconomic status is controlled for. A study in Germany found no systematic relationship between physician density and the quality of life (8).

A research group used 2008 inpatient data from the Wisconsin Hospital Association to identify all inflammatory bowel disease hospitalizations through ICD-9-CM discharge codes (9). County-level rates of primary care physicians and gastroenterologists were computed for each county using data from the American Medical Association and the US Census Bureau. It has been found that residence in counties with high physician density is associated with less complicated disease on hospitalization and lower hospitalization charges for inflammatory bowel disease.

Higher physician density has been associated with earlier stage of diagnosis of malignant melanoma, lower incidence of cervical cancer and earlier stage at diagnosis of breast cancer (10–13). It has been observed that higher gastroenterologist or primary care physicians density is associated with 14–17% lower incidence of late-stage colorectal cancer in non-metropolitan counties or those with low population density (2). One study pursued to calculate the effect of physician-specialty density on melanoma prognosis (14). A higher density of dermatologists was associated with better prognosis (lower mortality to incidence ratio). Internist density was also a significant predictor of better prognosis whereas increased family practitioner density was associated with worse prognosis. Another study investigated the effect of regional variations in the supply of health services on specific types of avoidable cancer deaths over 5 years using German districts as units of analysis (15). An increase in physician density tended to be associated with a small reduction in avoidable cancer death rates.

It appears that an increase in the physician density generally improves the quality of health care and should prevent suicides. However, several research reports suggest that of those people who committed suicide, up to two thirds saw a primary care physician within a month or less of their suicide completion (16–19). One research group even estimated this percentage to be three fourths (20). Only 36% of the physicians in the study of primary care physicians reported that they would conduct a suicide risk assessment when treating a patient presenting with major depression with moderate levels of severity (21).

The awareness of suicide as a major social and medical problem has increased significantly lately. However, many health care professionals who have frequent contact with high-risk patients do not have adequate training in suicide evaluation

techniques and treatment approaches to suicidal patients (22–24). Several studies in the US and UK have found that residency trainees, junior physicians and clinical psychology trainees report receiving limited training on the assessment and management of suicidal behavior (25–29). Regretfully, some physicians do not understand the clinical rationale for suicide risk assessment and the role they play in preventing suicidal behavior (30). The US Preventive Services Task Force believes that primary care providers should improve their knowledge and skills to be able to manage and assess suicide risk (31). Studies in Hungary, Sweden and Germany conducted over the past 30 years have shown that current methods of training of general practitioners in the recognition and management of suicidality are somewhat effective but not very effective (32–35). Medical students receive little training regarding suicide prevention and continuing education offerings for practicing physicians are few (36–39). However, even well-trained medical professionals frequently have problems assessing patients for suicidality and disagree in their evaluation of suicide risk (40).

Suicide prevention efforts among adolescents and young adults are restricted by the fact that there are many limitations related to the evaluation and management of suicidality in young people including the following (41):

- (a) Many clinicians underestimate the magnitude of the issue of suicidal behavior in adolescents and young adults and underestimate its prevalence;
- (b) There is a misconception that direct questioning of patients, including adolescents and young adults about suicidality is sufficient to estimate suicide risk;
- (c) Some medical professionals believe that adolescents and young adults with non-psychiatric illnesses do not need to be evaluated for suicidality which is a misconception;
- (d) Many health care professionals do not know about or underappreciate the role of contagion in suicidal behavior among young people; and
- (e) There is an erroneous belief that young men are at lower risk of suicide than young women.

In fact, male youth die by suicide over four times more frequently than female youth (42). It is important to note that young people usually visit physicians less frequently than individuals who are older.

We hypothesized that the physician density does not affect suicide rates among adolescents and young adults. To test this hypothesis, we examined the relation between physician density and suicide rates in adolescents and young adults in European countries.

17.2 Project

Information on suicide rates in 15–24-year-old and 25–34-year-old males and females was obtained from the World Health Organization (WHO) database (43). All European

countries for which the WHO data were available were included in the study. Thirty-eight countries were included in the inquiry: Albania, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Ukraine, and United Kingdom. The most recent available data were used. Information on the physician density in these countries was obtained from the US Central Intelligence Agency World Factbook (1).

Correlations were computed to examine relationships between suicide rates in 15–24-year-old and 25–34-year-old males and females and the physician's density in European countries. Countries were also divided into two groups, according to the median split of the physician density. Suicide rates among 15–24-year-old and 25–34-year-old males and females in these two groups were compared using the t-test. The SPSS program (version 19) was used to perform statistical analysis.

17.3 Findings

The raw data on the physician's density and suicide rates in 15–24-year-old and 25–34-year-old males and females in Europe are presented in Table 17.1. The general description of the sample is provided in Table 17.2. The highest physician density is in Greece (6.043 per 1,000 population) and the lowest physician density is in Albania (1.146 per 1,000 population). The highest suicide rate among 15–24-year-old males is in Russia (43.7 per 100,000 population per year). The highest suicide rate in females in the same age group is in Finland (8.7 per 100,000 population per year). Among 25–34-year-old males, the highest suicide rate is in Russia (70.9 per 100,000 population per year), and among 25–34-year-old females, the highest suicide rate was observed in Finland (12.1 per 100,000 population per year).

The correlation data are presented in Table 17.3. As expected, there were significant correlations between suicide rates in all four demographic groups. There were no correlations between physician density and suicide rates in any of four demographic groups. When the countries were divided, according to the median split into countries with higher and lower physician density, no difference with regard to suicide rates was found (see Table 17.4).

17.4 Discussion

The results of this study suggest that suicide rates are not related to physician density. This indicates that either physicians do not take an appropriate care of suicidal patients, or suicide is not preventable, or both.

Table 17.1: Physician density and suicide rates among adolescents and young adults in European countries

Country	Physician density (per 1,000 population)	Suicide rate among 15–24-year-old males (per 100,000 population per year)	Suicide rate among 15–24-year-old females (per 100,000 population per year)	Suicide rate among 25–34-year-old males (per 100,000 population per year)	Suicide rate among 25–34-year-old females (per 100,000 population per year)
Albania	1.146	5.5	4.9	4.4	4.0
Austria	4.749	13.8	2.2	18.0	3.3
Belarus	4.869	32.6	4.8	56.0	7.9
Belgium	2.987	15.3	4.2	28.2	7.0
Bosnia and Herzegovina	1.418	24.7	4.2	35.8	2.8
Bulgaria	3.635	9.5	2.1	10.3	3.8
Croatia	2.590	16.2	1.5	13.9	2.3
Czech Republic	3.625	11.8	2.5	22.6	2.2
Denmark	3.419	7.7	3.0	14.6	4.2
Estonia	3.409	28.4	5.1	23.9	4.2
Finland	2.735	26.4	8.7	34.4	12.1
France	3.497	9.9	2.9	21.5	5.1
Germany	3.531	9.2	2.4	12.7	3.2
Greece	6.043	2.7	0.3	6.6	1.4
Hungary	3.097	17.3	3.1	23.4	5.5
Iceland	3.934	16.6	0.0	19.5	8.8
Ireland	3.187	24.1	6.8	28.7	6.9
Italy	4.242	5.5	1.2	8.6	2.1
Latvia	2.988	22.3	1.8	40.4	5.0
Lithuania	3.664	41.3	6.3	50.0	6.6
Luxembourg	2.862	0.0	0.0	14.4	2.9
Macedonia	2.546	5.3	3.8	6.5	3.4
Malta	3.073	3.3	0.0	3.2	0.0
Moldova	2.668	15.1	2.7	28.3	2.9

(Continued)

Table 17.1: Physician density and suicide rates among adolescents and young adults in European countries (*Continued*)

Country	Physician density (per 1,000 population)	Suicide rate among 15–24-year-old males (per 100,000 population per year)	Suicide rate among 15–24-year-old females (per 100,000 population per year)	Suicide rate among 25–34-year-old males (per 100,000 population per year)	Suicide rate among 25–34-year-old females (per 100,000 population per year)
Netherlands	3.921	7.5	2.4	11.3	4.7
Norway	4.076	16.0	5.9	20.2	10.1
Poland	2.144	19.5	3.0	23.6	2.4
Portugal	3.755	6.7	1.4	9.2	2.0
Romania	1.916	10.5	2.6	15.8	1.9
Russia	4.309	43.7	7.4	70.9	9.0
Serbia	2.035	8.2	1.8	16.3	5.7
Slovak Republic	3.000	13.0	1.7	19.2	2.0
Slovenia	2.473	14.3	2.6	26.5	1.4
Spain	3.705	5.3	1.2	9.6	2.3
Sweden	3.583	15.5	6.8	16.4	7.5
Switzerland	4.070	16.2	8.2	16.2	6.4
Ukraine	3.125	26.5	4.5	42.5	5.3
United Kingdom	2.739	7.9	2.1	13.8	3.4

Table 17.2: Description of the study sample

	N	Minimum	Maximum	Mean	Standard deviation
Physicians' density (per 1,000 population)	38	1.146	6.043	3.283	0.949
Suicide rate among 15–24-year-old males (per 100,000 population per year)	38	0.000	43.700	15.139	10.150
Suicide rate among 15–24-year-old females (per 100,000 population per year)	38	0.000	8.700	3.318	2.290
Suicide rate among 25–34-year-old males (per 100,000 population per year)	38	3.200	70.900	22.037	14.683
Suicide rate among 25–34-year-old females (per 100,000 population per year)	38	0.000	12.100	4.518	2.704

Table 17.3: Correlations between physicians' density and suicide rates among adolescent and young adults in European countries

	Physicians' density (per 1,000 population)	Suicide rate among 15–24-year-old males (per 100,000 population per year)	Suicide rate among 15–24-year-old females (per 100,000 population per year)	Suicide rate among 25–34-year-old males (per 100,000 population per year)	Suicide rate among 25–34-year-old females (per 100,000 population per year)
Physicians' density (per 1,000 population)	1.000	0.078	-0.034	0.094	0.173
	Pearson correlation	0.640	0.840	0.575	0.300
	Sig. (2-tailed)	38	38	38	38
Suicide rate among 15–24-year-old males (per 100,000 population per year)	0.078	1	0.659	0.914	0.575
	Pearson correlation	38	<0.001	<0.001	<0.001
	Sig. (2-tailed)	38	38	38	38
Suicide rate among 15–24-year-old females (per 100,000 population per year)	-0.034	0.659	1.000	0.521	0.698
	Pearson correlation	<0.001	38	0.001	<0.001
	Sig. (2-tailed)	38	38	38	38
Suicide rate among 25–34-year-old males (per 100,000 population per year)	0.094	0.914	0.521	1.000	0.528
	Pearson correlation	<0.001	0.001	0.001	0.001
	Sig. (2-tailed)	38	38	38	38
Suicide rate among 25–34-year-old females (per 100,000 population per year)	0.173	0.575	0.698	0.528	1.000
	Pearson correlation	<0.001	<0.001	0.001	0.001
	Sig. (2-tailed)	38	38	38	38

Table 17.4: Comparison of suicide rates in countries with higher and lower physicians' density

	Higher physician's density		Lower physician's density		Analysis		
	Mean	SD	Mean	SD	t	df	p
Suicide rate among 15–24-year-old males (per 100,000 population per year)	15.78	12.05	14.49	8.10	-0.39	36	0.70
Suicide rate among 15–24-year-old females (per 100,000 population per year)	3.48	2.48	3.16	2.13	-0.043	36	0.67
Suicide rate among 25–34-year-old males (per 100,000 population per year)	22.00	17.56	22.07	11.60	0.01	36	0.99
Suicide rate among 25–34-year-old females (per 100,000 population per year)	4.99	2.69	4.05	2.70	-1.08	36	0.29

Do physicians fail to recognize significant clues to suicide?

The rates of visits to primary care physicians preceding suicide completion are much higher than the rates of visits to mental health specialists, giving primary care physicians/pediatricians a significant and important role in suicide prevention (16–21). However, it has been observed that physicians tend to provide less than quality care, as measured by conducting a suicide risk assessment, for patients who present with depressive symptoms (20).

Possibly, physicians fail to forestall preventable deaths. Adolescents are often at risk of suicide because of stresses of puberty and approaching adulthood. Prolonged loss of sleep, intake of alcohol and drugs may result in loss of controls over self-destructive impulses. The management of suicidal adolescents and young adults includes diagnosis and treatment of existing psychiatric illnesses, assessment of suicide risk, and the reduction of access to highly lethal methods for committing suicide, such as guns (44). Collateral reports from parents, spouses, partners, family members, or friends can provide valuable information to clinicians. A physician may fail to take appropriate steps if his personal and cultural attitudes toward suicide and professional incompetence make him deny to himself that suicidal act is possible or imminent. A physician needs attention, sensitivity and intuition in listening for and responding to a distressed appeal for help, and a non-judgmental approach in dealing with suicidal patients, particularly with adolescents and young adults.

Is suicide preventable?

Health care professionals deal with almost no other event as rare as suicide. Although suicidal ideation and attempts are associated with elevated suicide risk, most individuals with suicidal thoughts or attempts will never commit suicide. Suicide attempts and ideation occur in about 0.7% and 5.6%, respectively, of the general US population (45). In comparison, in the US the annual incidence of suicide in the general population is about 11 suicides for every 100,000 persons, or 0.011% of the total population per year (46). Even under the best conditions, the attempted prediction of a rare behavior such as suicide inevitably generates a very large number of false-positive and false-negative cases (47). It has been shown that for realistic assumptions of sensitivity and specificity, a screening test for suicide risk would have a positive predictive value of 0.3% and generate a vast number of false positives (47). Besides, the prediction of suicidal behavior is based on inexact criteria that are inadequate at predicting the behavior of a given person, and suicidal individuals often hide or deny suicidal thoughts in order to evade unwanted intervention efforts, such as involuntary hospitalization. Clearly, it is very difficult to predict and prevent suicide in any age group.

Limitations

The results of this study should be treated with caution, because many confounding variables are not taken into account. For example, prevalence of psychiatric illnesses, especially depression and alcohol abuse, socioeconomic factors, divorce rates, and cultural aspects may affect suicide rates (48–50).

Conclusive remarks

It is unclear what educational measures or interventions may be the answer to having a positive impact on the long observed low quality of suicide risk assessment by primary care and specialty physicians. Regrettably, even psychiatrists sometimes do not perform an appropriate suicide risk assessment.

Physicians should be aware of and use published suicide prevention guidelines for patient care. The training of physicians including pediatricians with regard to suicide prevention and management of suicidal patients should be improved. Continuing education on suicide should be required. Physicians should use a screening instrument for suicide assessment with all of their patients, especially those from at-risk or vulnerable populations such as older adults or patients with pain.

It is essential to note that our concern about prediction of suicide is related to our inability to prevent all suicides (51). Absence of suicide produces no data. If suicide is difficult to predict, its prevention is even more difficult to notice. Possibly, many suicidal individuals are recognized and successfully treated.

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18 Suicidal behavior in Indian adolescents

Diana Samuel and Leo Sher

Suicide is both a public and mental health problem as it is a leading cause of deaths, especially among adolescents. Two factors that contribute to adolescents who commit suicide are having a primary mood disorder and/or substance use. In the Indian culture, the family unit has both a positive and negative impact on suicide. The family serves as a protective factor providing a strong support for the individual, but alternately creating an inseparable individual when seeking mental health care which often complicates the situation. Due to the stigma, Indians typically perceive having a mental illness as shameful. Religion is integral to the Indian culture so much so that individuals often use herbal remedies, seek help from religious leaders and attend religious establishments prior to obtaining a mental health evaluation in those that were subsequently deemed as mentally ill. Despite suicides being underreported and misdiagnosed in India, the highest rates are among those less than 30 years old. The methods most commonly used to commit suicide in India include use of poison (often pesticides), hanging, burning and drowning. When immigrating, Indians tend to switch the methods they use to commit suicide from use of poison to hanging which may reflect a lack of availability of poison or the influence of the host culture. Considering the high suicide rates in adolescents, the importance of providing psychoeducation, restricting access to lethal means, and promoting social integration in immigrants are ways we may be able to help prevent suicides in Indian adolescents.

18.1 Introduction

Suicide is the act of intentionally causing one's own death. Suicide attempts as defined by Kar are "any act of self-damage inflicted with self-destructive intentions" (1). The factors that contribute to any particular suicide are diverse and complex. Considering that suicide is the third leading cause of death among those between the ages of 15–24 years (2), it is one that must be explored further. In 2011, in the US alone, 15.8% of high school students had seriously considered attempting suicide during the 12 months before the survey (3). During the same time, 12.8% of students had made a plan of how they would commit suicide and 7.8% had attempted suicide at least once (3). Approximately 50–75% of children and adolescents who commit suicide have had a mood disorder, most commonly major depression (4). About one quarter to two-thirds of adolescents who commit suicide received a diagnosis of substance abuse or dependence (5, 6). The stigma associated with mental illness is often a significant barrier to obtaining psychiatric care. When considering the limited mental health resources in countries such as India, it is not surprising that suicide rates for instance may be underreported and/or misclassified in order to prevent further shame to the

family. Despite the continuous and growing impact of urbanization, secularization, and Westernization, the traditional joint household, both in ideal and in practice, remains the primary social force in the lives of most Indians.

18.2 Indian psyche

Indian psyche is distinct as it has been influenced by various invaders into the country, collectivism and interdependence (7). In India, people learn the essential themes of cultural life within the bosom of a family. In most of the country, the basic units of society are the patrilineal family unit and wider kinship groupings. The most widely desired residential unit is the joint family, ideally consisting of three or four patrilineally related generations, all living under one roof, working, eating, worshiping, and cooperating together in mutually beneficial social and economic activities. Patrilineal joint families include men related through the male lineage, along with their wives and children. Most young women expect to live with their husband's relatives after marriage, while retaining important bonds with their biological families. Indians consider the relationships within a family very intimate, spread over several people including grandparents, parents, uncles, aunts and siblings, thus often making the parents not the sole guardians of the child (7). With age, a series of similar relationships of varying intensities and duration develop and most often, consequently most Indians do not assume full individuality (7). Therefore, unlike the self-reliant, independent nature that is most often nurtured and even idealized in individuals of the Western world, one of the core values of Indians is based on intimacy, family security and its stability (7). The emotional interdependence that family members feel with each other is often so intense that the family becomes almost an organic unit. Ego boundaries are permeable to others in the family, and any notion of a separate self is often dominated by a sense of what psychoanalyst Alan Roland has termed a more inclusive "familial self." Interpersonal empathy, closeness, loyalty, and interdependency are all crucial to life within the family. It is the intimate nature of the family unit that forms a practically inseparable identity from the individual making it impossible to separate when attempting to treat a person with mental illness (7).

Nonetheless, it is this same family that provides the support that is protective against suicide. Family support has been shown to be a positive factor for those that are at risk for suicide and also integral in the treatment of these individuals. In one study of adolescents that were at risk for suicide in US adolescents with higher levels of family support had significantly higher levels of self-esteem and self-esteem was found to be a protective factor against suicide (8). Self-esteem is formed when one recognizes themselves as competent and worthy which subsequently creates a sense of self-acceptance, self-respect, and satisfaction with one's self and life (8). Feeling connected to the family may reduce feelings of social isolation and loneliness which are often antecedents to suicide behaviors. Family support creates a feeling that

one is cared for, wanted and loved by its members which diminishes the likelihood that an adolescent will consider suicide as a “rational” alternative for solving their problems (9).

Religion is an integral aspect of life in India, so far as that religious prayers and healers often play a role in the treatment of all illnesses, including mental illness (10). In one study, it was found that ninety percent of the time that those who were studied had experienced any type of symptom of illness, they initially relied entirely on home remedies and other forms of self-treatment (11). This implies that religious beliefs impact the way one perceives illness in India, whether it be physical or mental ailments. In addition to one’s religion, educational level, caste and social class, religious affiliation as well as religious attendance affected the psychiatric care sought by those individuals (10). In a study conducted in North India, 84% of patients eventually seen in a psychiatric institution had been to a local temple prior to obtaining treatment (12) which may be due to having a poor understanding of mental illness or rather a denial of the actual illness. In terms of those people that saw religious healers for mental illness prior to seeking an official psychiatric consultation, the highest rates of psychiatric diagnoses were in the group diagnosed as having schizophrenia and delusional disorders (10). This implies that many individuals with chronic mental illness may not initially recognize their psychiatric illness as being purely psychiatric or they may feel that their illness is better treated through religious means, at least initially.

18.3 Suicide in India

The Indian subcontinent encompasses eight distinct countries, India, Pakistan, Afghanistan, Sri Lanka, Bangladesh, Nepal, Bhutan, and the Maldives and collectively, these countries comprise 1.3 billion people. Information gathered on suicide on the Indian subcontinent comes mainly from India, Sri Lanka and Pakistan as the remaining countries have poorly developed mental health services and consequently, mental health issues including suicide is given little importance when compared to other priorities such as infectious diseases and sanitation. Some of the problems in obtaining records for suicides in countries of the Indian subcontinent include legal, social and religious reasons (13). For example, suicide is considered a criminal act in Pakistan and punishable with a jail term and heavy financial penalty. This has led to both suicides and attempted suicides being underdiagnosed and underreported (14). Until 1994, attempting suicide was a punishable act in India (13). Under section 309 of the Indian Penal Code from 1833 it states, “Whoever attempts to commit suicide and does any act towards the commission of such an offence shall be punished with simple imprisonment for a term which may extend to 1 year, or with a fine or with both” (15). It was only in 1994 that the Supreme Court of India found this code was unconstitutional and Justice Rajinder Sachar of the Delhi High Court said in his

judgment: “Instead of society hanging its head in shame that there should be such social strains that a young man should be driven to commit suicide, it compounds its inadequacy by treating the boy as a criminal. Instead of sending him to the psychiatric clinic it gleefully sends him to mingle with criminals, as if trying its best to see that in future he does fall foul of the punitive section of the Penal Code” (15). In 1996, the Supreme Court held that the right to life in Article 21 of the Constitution did not include the right to die and court struck down Section 309 of the Penal as being a violation of Article 21 and thus unconstitutional (15). Therefore, suicide attempts and the abetting of suicide continue to be misdemeanors in India and a person convicted of an offense of attempted suicide may be indicted to imprisonment for a term not exceeding 1 year, or a fine, or both (15).

From 1978 to 1990, there was an increase of 41.3% in suicide from 6.4 to 8.9 (per 100,000). This attributes to a growth rate of 4.1% per year from 1980 to 1990 in suicide. This rate of suicide increase in India during this time is comparable with the global increase in suicide during the same time (16). In 2008, 125,017 people were recorded to have committed suicide, which was a 1.9% increase from the previous year of 122,637 suicides (17). Even within India there are wide variations in the suicide rates such that the southern states (Kerala, Karnataka, Andhra Pradesh and Tamil Nadu) having a rate greater than 15 per 100,000 while in the northern states (Punjab, Uttar Pradesh, Bihar and Jammu and Kashmir) the suicide rate is less than 3 per 100,000 (18). This pattern has remained stable within the last 20 years. Some factors that may contribute to this variation are that in the southern states, there is higher literacy, better reporting system, and higher socioeconomic status (18).

The highest percentage of people who commit suicide in India (37.8%) are below 30 years of age (19). One out of every three of reported suicides every 15 minutes in India were committed by a youth between the ages of 15–29 (19). Kerala, well-known for being India’s first fully literate state, has the highest number of suicides with 32 people committing suicide in this state every day (19). Compared to the US where the overall rate of suicide is about 11 deaths per 100,000 persons, it remains slightly higher than the 10.5 suicides reported in India (20, 21). However, this difference may be better attributed to underreporting rather than a true difference according to many studies, but is unclear.

Due to the stigma associated with mental illness, it is thought that the actual suicide rate in India may be higher than that reported due to concern about the harm to family reputation or police involvement (22). In 2010, it was reported that 33.1% of suicides were accounted for by ingestion of poison, 31.4% by hanging, 8.8% by fire/“self-immolation” and 6.2% by drowning (23). Also, it is possible and questionable whether the suicides recorded as acts of “self-immolation” may be underestimated and that those deaths reported as accidental deaths due to fire may be due to suicides (22). It has been suggested that the annual suicide rate could be six to nine times the official rate (18) which is likely due to non-reporting, underreporting and misclassification due to stigmas, religious sanctions, legal issues and insufficient registration systems (24).

Burning has also been a method used as a means of successful suicide among young women (16) with about 30% of immigrant Indians committing suicide by burning (25). A suicidology study, conducted from March to October of 1988 in a Madurai Hospital in India of 100 cases of consecutive burn victims, found that the majority of these cases were caused by suicide and found to be grouped into three categories—those with marital problems (36/100), other stressful family and life circumstances (26/100), and dowry related problems (5/100) (16). This information was gathered by contacting the survivors of suicide attempts, family members of those who committed suicide, in addition to the Department of Plastic Surgery and Forensic medicine reviewing each case individually and deciding whether they were likely accidental, suicidal or homicidal (16). One of the differences found between the accidental versus suicidal burns were that 15 of the cases were mentally ill in the suicidal group while only three in the accidental group. Among the suicide group, eight cases had made prior suicide attempts but not by burn injury (two of which were psychiatrically ill, and other two who were physically ill) (16). This suggests that in India like many other countries, suicide is associated with psychiatric pathology.

18.3.1 Adolescent suicide in India

In India, each year greater than 100,000 people commit suicide with a gradual upward trend being noted (17). With the highest percentage of those being below the age of 30, accounting for about 37% of all suicides in India in 2009 (19, 21) it is important to identify factors that may differentiate this group. In a study of 149 suicide attempters, adolescents differentiated themselves from the other age groups in that 90% of them made their attempts impulsively with only 9% of the attempts being of high potential in terms of risk (26). Within this adolescent population, the most common predisposing factor to suicide was reported childhood trauma while mental illness was the least when compared to other age groups (27). In addition, all of these adolescents reported experiencing negative life events (27), which typically included failing examinations and minor violations of discipline with anticipation of negative consequences (27, 28). Among the listed reasons, “illness,” “family problems,” and “failure in examination” were the main reasons for suicide among children (23). In comparison, adults that attempted suicides typically had an underlying psychiatric illness and the methods they used were considered more serious attempts, while suicide attempts by adolescents in India were more impulsive and due to “anomalous life conditions” (1).

18.3.2 Immigration and suicide

Although there are no studies found that specifically examined adolescent suicide among Indian adolescents in the US, one study published in the *British Journal*

of Psychiatry looked at the suicide patterns among immigrants in Britain that immigrated from the Indian subcontinent. From 1970 to 1978, it was found that 145 Indian men and 86 Indian women committed suicide in England and Wales which accounted for 1.8% of male death and 2.7% of female death among Indians in England and Wales (25). When compared to the same period and rates of suicide in England and Wales, only 0.8% and 0.6% respectively of male and female deaths were accounted for by suicide (25). Among both genders, suicide mortality was higher among young Indians, specifically Indian women between the ages of 15–24 who had over an 80% higher suicide rate than women of corresponding ages (25).

When individuals from different cultures immigrate to a host country, the immigrants assume similar suicide rates and methods to members of the host culture (29). Generally, suicide rates among first generation immigrants are lower and most resemble rates typical of their country of origin (30) with subsequent generations have increased rates comparable to North American trends (31). Some factors that contribute to assimilation and may impact these rates include acculturative stress, process of acculturation, risk factors (i.e., single, drug use and rejection by host culture) and protective factors (family support, belonging to an ethnic community, being married, living in a large city) (29). The stress associated with immigration, whether or not there is an underlying mental illness, can lead to severe and possibly chronic behavioral issues including alcohol and illicit drug abuse, depression, anxiety, and posttraumatic stress disorder which subsequently place these individuals at higher risk for suicide (32). First generation immigrant populations within North America tend to choose methods of suicide that are influenced by their cultural heritage (29), however, it was noted that Indian immigrants tend to switch methods of suicide from poisoning with pesticides to hanging, which may reflect the lack of availability of pesticides in the host countries or may indicate that the host culture has an influence on the immigrant (33).

18.3.3 Preventing suicidal behavior in Indian adolescents

For many who engage in suicidal behavior, there is often an appropriate alternative resolution to the precipitating problems that lead to suicide (18). Non-governmental organizations (NGOs) are a large support system that should be used to help support suicidal individuals (18). NGOs can serve not only as an entry point for individuals requiring professional services, but also provide education, raise awareness in the public and establish intervention programs (18). Reducing access to lethal means including pesticide and alcohol which are associated with high rates of suicide in India would be part of the national plan for suicide prevention (18). Encouraging and promoting responsible reporting of suicide and issues relating to suicide, supporting NGOs, improving the capacity of primary care workers and mental health specialists, and providing support for those who suffer from the loss of someone who

committed suicide should all be part of the solution to preventing suicide in India (18). In general, an overall improvement in psychoeducation and subsequent increased awareness of people in the community concerning mental illness would likely decrease the stigma and hopefully improve suicide outcomes.

Features of impulsivity which include poor impulse control, quick provocation, and disregard of external constraints are at higher levels at age 17 and with a slower decline with age in those who attempted suicide when compared to non-attempters (34). Therefore, it is imperative that public health interventions such as restricting access to pesticides (35), increased surveillance, training and community action on the use of pesticides (i.e., safe storage and proper dilutions) (36), and stricter alcohol laws may prevent many deaths caused by suicide in India. Secondary prevention is also very important and includes recognizing and treating psychiatric disorders, particularly mood disorders and alcohol abuse (37) which would also decrease suicide risk.

The well-known theory by Emile Durkheim stresses the importance of community and social networking as being protective against suicide (38). He felt that difference in suicide rates seen between cultures was an inverse function of the level of social integration, such that individuals with strong social bonds had a lower risk for suicide than those with less developed networks. Supporting this theory, living in a large city is protective against suicide. Factors that need to be strengthened in Indian adolescents that immigrate to another country are maintaining culture and establishing an ethnic community (29). It is this ethnic community that appears to similarly serve as the family unit for immigrants.

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19 American juvenile justice system: history in the making

Aaron Meng, Roland Segal and Eric Boden

The original theory behind separating juvenile offenders from adult offenders was to provide care and direction for youngsters instead of isolation and punishment. This idea took hold in the 19th century and became mainstream by the early 20th century. In the 1950s and 1960s, public concern grew because of perceived lack of effectiveness and lack of rights. The Supreme Court made a series of rulings solidifying juvenile rights including the right to receive notice of charges, right to have an attorney, and proof of beyond a reasonable doubt. In the 1980s, the public view was that the juvenile court system was too lenient and that juvenile crimes were on the rise. In the 1990s, many states passed punitive laws, including mandatory sentencing and blanket transfers to adult courts for certain crimes. As a result, the pendulum is now swinging back toward the middle from rehabilitation toward punishment.

19.1 Introduction

The economic developments of the 19th century brought the legal status of children to the public's eye. The first years of the 1800s were characterized by expansionary fiscal policy. The country was booming and the government was spending freely on infrastructure improvements and real estate speculation, increasing banking activity. By 1818, Americans began to lose confidence in the banks, forcing the government to begin to contract the economy. This economic slowdown intensified, and in 1819, the US plunged into its first true economic crisis, the Great Panic of 1819 (1). This crisis forced most children factory workers out of their jobs and into a state of unsupervised inactivity. Concern about these children began the transformation of social safety net institutions to institutions designed to help these children. In 1824, in New York City, the Society for Prevention of Pauperism became the Society for Reformation of Juvenile Delinquents. This Society opened the first "House of Refuge" in US in 1825, followed by similar agencies in Boston and Philadelphia in 1828. These institutions were designed to prevent civil unrest by maintaining class status (2).

The purpose of these juvenile facilities, a.k.a. training schools, was to isolate the juvenile delinquents from the corruption of hardened adult criminals, and to provide them discipline and guidance. A large part of the adjudicated minor's daily schedule was devoted to supervised labor for the purpose of education and discipline, but also to support the operating expenses. In addition, students were taught literacy and religion. Today's training schools continue to house a large number of juvenile offenders. However, over the years, the emphasis changed toward recovery with individualized diagnosis and treatment, improved education, and rehabilitation services (3).

Later in the 19th century, the Industrial Age transformed the workplace to one in which workers required an increasingly complex skill set (4). Manufacturing began focusing on production of interchangeable parts with repeatable precision and mass production. With steam power, electrical power and internal combustion engines came the use of production machinery that required specific learned skill sets to operate (5). As these skills took time to acquire, youths required a longer transition between childhood and working adulthood. Thus the concept of adolescence began to develop, and so did the idea that the responsibilities of this newly defined demographic should be different from those of adults. In what is now known as the Progressive Era, laws were enacted requiring school attendance, limiting the hours of employment, and increasing the age at which one could marry (4). During this time period, more parents began working outside of the home and, therefore, could not home-school their children. The burden of educating children, both academically and socially, then fell upon the school system (6).

Prior to this Progressive Era, there was no separate juvenile justice system, and juvenile offenders were prosecuted under the same criminal law constructs as adults (7). Some additional protections were afforded to youths, however, as immaturity could be used to reduce culpability. For example, depending on jurisdiction, “infancy” was considered an absolute defense until the age of 7 or 10 years. After that, there was a presumption that a youth was incapable of forming criminal intent until the age of 14 years. This presumption could be rebutted if the prosecution could present sufficient evidence of maturity (8, 9). Children fourteen and older were presumed capable of understanding wrongfulness, but the defense could rebut this presumption by establishing immaturity (10).

19.2 Juvenile courts

In 1899, the nation’s first juvenile court was established in Cook County, Illinois (11). In the first juvenile courts, instead of the adversarial trials of adult courts which sought an answer of guilt versus innocence, judges investigated the character and social background of children. They attempted to interpret the reasons and motivations behind the children’s actions to help determine their moral character (12). Instead of using the terminology of guilt, innocence, trial or sentence, these courts spoke of adjudication and disposition. Instead of focusing on the offense at hand, they focused on the best interests of the juvenile (13). These courts began to distance themselves from adult criminal courts by seeking rehabilitation for youths rather than punishment (12).

Since the objective was treatment, the proceedings of these courts differed significantly from criminal courts. Due process and rules of evidence were viewed as unnecessary and possibly detrimental to the goal of assisting the wayward youths. With the key question being amenability to treatment, rather than culpability, social

workers, probation officers, and mental health professionals played key roles, as they were best equipped to answer the question at hand (8).

Additionally, children could be adjudicated for “status offenses,” behaviors that were illegal for a person under the age of 18 years, but legal if committed by an adult. These offenses included sexual acts, alcohol consumption, smoking cigarettes, running away, and truancy. Under the public policy of *parens patriae* (the power of the state to protect the individuals who need protection), the juvenile courts were given control over all juvenile matters, both delinquent (i.e., criminal) and status offense. Unfortunately, children were often adjudicated into reform schools for both delinquent matters and status offenses for unreasonable durations without due process (14). Children could also be adjudicated for “pre-delinquency” even if no crime was yet committed, as long as they had caused trouble for an authority figure (15).

In 1974, the National Juvenile Justice and Delinquency Prevention Act was enacted. The purpose of this act was to give the states money in order to enact four core items: (a) the deinstitutionalization of juvenile status offenders from detention centers and jails, (b) the provision of “sight and sound” separation between juvenile and adult offenders, (c) the prevention imprisonment of youth in adult jails, and (d) an investigation of the issue of over-representation of minorities in the justice system (16).

19.3 The Supreme Court of the United States' role in defining the juvenile justice system

The US Supreme Court noticed the imbalance in juvenile rights and responded. In 1966, *Kent v. United States* began a surge of reformations aimed at providing juveniles rights similar to defendants in criminal courts. The petitioner in *Kent v. United States* was a 16-year-old male who was arrested for charges of housebreaking, robbery, and rape. As a 16-year-old, he was subject to the jurisdiction of the juvenile court unless after a “full investigation,” that court waived jurisdiction and remanded him to the District Court for trial. He was waived to the District Court after a “full investigation,” but without due process. He moved to dismiss this indictment and was overruled. The US Court of Appeals upheld this decision, but the US Supreme Court reversed the decision, stating that due process and assistance of counsel are necessary in order for such a waiver to occur. Justice Fortas said, “... the child receives the worst of both worlds: he gets neither the protections accorded to adults nor the solicitous care and regenerative treatment postulated for children” (17, 18).

A year later, the US Supreme Court expanded the rights of minors facing charges in their decision on the case of *In re Gault*. Gerald Gault was a 15-year-old male who was brought into custody for making obscene phone calls. His parents were not notified of his arrest, they were not officially notified of his charges, and he was not given an opportunity to confront his accuser. Despite the lack of due process, Gault was

committed to the State Industrial School for 6 years as a juvenile delinquent. The US Supreme Court opined that in most cases the Constitutional protections afforded to adults facing criminal charges should also apply to youths. As such, juveniles had a right to be advised of their right to counsel, have timely notice of their hearings, cross-examine witnesses testifying against them, and invoke their right against self-incrimination (17, 19).

In 1969, the Supreme Court heard a case in which Samuel Winship, a 12-year-old, was charged as a juvenile delinquent for stealing \$112 from a woman's purse. In the New York Family Court, at that time, the standard for proving a juvenile's guilt was based on "preponderance of evidence" (i.e., more likely than not). Using this standard, Winship was found guilty, even though the Family Court acknowledged that the evidence against Winship would not meet the standard of "beyond a reasonable doubt," the much higher standard used in criminal courts. The Supreme Court ruled that the standard of "beyond a reasonable doubt" must be used in all criminal cases, both for adults and for juveniles (17, 20).

Despite the changes that occurred from these cases, the US Supreme Court continued to support significant differences between juvenile adjudication courts and adult criminal courts. For example, the Supreme Court drew the line at the right to jury trials for youths in *McKeiver v. Pennsylvania* in 1971. Justice Harry Blackmun wrote that juveniles were entitled to some, but not all of the Constitutional rights of adults in the criminal justice process (17, 21).

In 1975, The Supreme Court upheld the ideal that the juvenile justice system was a more benevolent entity than the adult justice system, and that it offered significant social benefits. Through their decision in *Breed v. Jones*, the Court gave youths the protection against double jeopardy in transfers to adult courts and opined that having such waiver hearings prior to adjudication hearings would not unduly strain the juvenile justice system (17, 22).

The US Supreme Court, focused on the Eighth Amendment of the US Constitution. In the 2002 case of *Atkins v. Virginia* the US Supreme Court opined that it is cruel and unusual to execute mentally retarded individuals. The justices cited the "evolving standards of decency." Based on that standard, in the 2005 case of *Roper v. Simmons*, the Supreme Court of US held that it is unconstitutional to impose death sentence if the perpetrator was less than 18 years of age at the time of the crime (23).

19.4 More recent changes

In the late 1980s, there was a significant increase in lethal violence perpetrated by youths. By 1994, homicides and aggravated assaults committed by teens aged 13–17 years more than doubled. School violence in the suburbs and small towns nationwide was also on the rise (24). Public opinion is a major driving

force in democratic societies. In 1991, the general opinion was that juveniles who committed seriously violent offences should be punished. However, the majority of people did not think that incarceration of juvenile offenders in adult facilities was appropriate. Public opinion changed, however in the early 21st century, when a public poll showed that the majority of respondents favored treating violent, juvenile offenders between the ages of 14 and 17 the same as adults (8). The legislatures in most states responded to the public opinion that juvenile crime had reached epidemic proportions by increasingly modeling their juvenile justice system after their adult criminal systems. This resulted in lowering the age and broadening the offense criteria for trying teenagers in adult criminal court as opposed to juvenile court (24).

19.5 Current controversies

Juvenile justice is a complex issue that spans many boundaries and touches many lives. As long as we are open to discuss the controversies that exist within the system we will be able to improve on what we currently have.

One of these controversies is the question of whether lack of punishment is a cause of the increase in juvenile violent crimes. During the period between 1970s and 1990s, the juvenile justice system became more adjudicative than punitive. During the same period, rates of juvenile violent crimes had grown almost twice as fast as the adult crime rates (25).

Another controversy is about blanket provisions that transfer juvenile offenders from the juvenile to the adult justice system for certain charges (26). Currently 23 states do not specify a minimum age for transfer to adult court for one or more offense classifications. In addition, 46 states allow the transfer of a case into the adult criminal system based on the type of the offense (27).

Yet another controversy is whether juvenile status offense laws are justified or if they should be abolished. Many behavioral health experts believe that status offense behaviors are precursors to more serious crimes (13).

19.6 Summary

From its beginnings within the same framework as the adult criminal code, to the reformations that attempted to transform the system into a therapeutic rather than punitive entity, and more recently the shift back to increased punishment, the juvenile justice system of US has been in a state of frequent flux. The current controversies and varying opinions as to whether a more punitive or more therapeutic approach should prevail will likely continue this trend of change.

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Section VIII: **Acknowledgements**

20 About the editors

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21 About Icahn School of Medicine at Mount Sinai and the James J. Peters Veterans' Administration Medical Center, New York City, United States

Icahn School of Medicine at Mount Sinai was established in 1968. The medical school is noted for innovation in education, biomedical research, clinical care delivery and local and global community service. Icahn School of Medicine at Mount Sinai is in the top-tier of programs in the United States, currently ranked 18th overall in the 2012 edition of US News and World Report best medical schools for research and no other medical school in the US has risen so quickly over the past decade. It has more than 3,400 faculty in 32 departments and 14 research institutes.

The James J Peters Veterans' Administration (VA) Medical Center is the oldest VA facility in New York City, celebrating over 75 years service to veterans. It is a tertiary care hospital affiliated with Mount Sinai School of Medicine. The Medical Center provides a full range of patient care services, with state-of-the-art technology as well as education and research. Comprehensive health care is provided through primary care, tertiary care, and long-term care in areas of medicine, surgery, psychiatry, physical medicine and rehabilitation, neurology, oncology, dentistry, geriatrics and extended care.

22 About the National Institute of Child Health and Human Development in Israel

The National Institute of Child Health and Human Development (NICHD) in Israel was established in 1998 as a virtual institute under the auspices of the Medical Director, Ministry of Social Affairs and Social Services in order to function as the research arm for the Office of the Medical Director. In 1998 the National Council for Child Health and Pediatrics, Ministry of Health and in 1999 the Director General and Deputy Director General of the Ministry of Health endorsed the establishment of the NICHD.

22.1 Mission

The mission of a National Institute for Child Health and Human Development in Israel is to provide an academic focal point for the scholarly interdisciplinary study of child life, health, public health, welfare, disability, rehabilitation, intellectual disability and related aspects of human development. This mission includes research, teaching, clinical work, information and public service activities in the field of child health and human development.

22.2 Service and academic activities

Over the years many activities became focused in the South of Israel due to collaboration with various professionals at the Faculty of Health Sciences (FOHS) at the Ben Gurion University of the Negev (BGU). Since 2000, an affiliation with the Zusman Child Development Center at the Pediatric Division of Soroka University Medical Center has resulted in collaboration around the establishment of the Down Syndrome Clinic at that center. In 2002, a full course on “Disability” was established at the Recanati School for Allied Professions in the Community, FOHS, BGU and in 2005 collaboration was started with the Primary Care Unit of the faculty and disability became part of the master of public health course on “Children and society.” In the academic year 2005–2006, a one semester course on “Aging with disability” was started as part of the master of science program in gerontology in our collaboration with the Center for Multidisciplinary Research in Aging. In 2010 collaborations with the Division of Pediatrics, Hadassah Medical Center, Hebrew University, Jerusalem, Israel.

22.3 Research activities

The affiliated staff have over the years published work from projects and research activities in this national and international collaboration. In the year 2000, the

International Journal of Adolescent Medicine and Health and in 2005 the *International Journal on Disability and Human Development* of De Gruyter Publishing House (Berlin and New York), in the year 2003 the *TSW-Child Health and Human Development* and in 2006 the *TSW-Holistic Health and Medicine of the Scientific World Journal* (New York and Kirkkonummi, Finland), all peer-reviewed international journals were affiliated with the National Institute of Child Health and Human Development. From 2008 also the *International Journal of Child Health and Human Development* (Nova Science, New York), the *International Journal of Child and Adolescent Health* (Nova Science) and the *Journal of Pain Management* (Nova Science) affiliated and from 2009 the *International Public Health Journal* (Nova Science) and *Journal of Alternative Medicine Research* (Nova Science).

22.4 National collaborations

Nationally the NICHD works in collaboration with the Faculty of Health Sciences, Ben Gurion University of the Negev; Department of Physical Therapy, Sackler School of Medicine, Tel Aviv University; Autism Center, Assaf HaRofeh Medical Center; National Rett and PKU Centers at Chaim Sheba Medical Center, Tel HaShomer; Department of Physiotherapy, Haifa University; Department of Education, Bar Ilan University, Ramat Gan, Faculty of Social Sciences and Health Sciences; College of Judea and Samaria in Ariel and in 2011 affiliation with Center for Pediatric Chronic Diseases and Center for Down Syndrome, Department of Pediatrics, Hadassah-Hebrew University Medical Center, Mount Scopus Campus, Jerusalem.

22.5 International collaborations

Internationally with the Department of Disability and Human Development, College of Applied Health Sciences, University of Illinois at Chicago; Strong Center for Developmental Disabilities, Golisano Children's Hospital at Strong, University of Rochester School of Medicine and Dentistry, New York; Centre on Intellectual Disabilities, University of Albany, New York; Centre for Chronic Disease Prevention and Control, Health Canada, Ottawa; Chandler Medical Center and Children's Hospital, Kentucky Children's Hospital, Section of Adolescent Medicine, University of Kentucky, Lexington; Chronic Disease Prevention and Control Research Center, Baylor College of Medicine, Houston; Division of Neuroscience, Department of Psychiatry, Columbia University, New York; Institute for the Study of Disadvantage and Disability, Atlanta; Center for Autism and Related Disorders, Department Psychiatry, Children's Hospital Boston, Boston; Department of Paediatrics, Child Health and Adolescent Medicine, Children's Hospital at Westmead, Westmead, Australia; International Centre for the Study of Occupational and Mental Health, Düsseldorf, Germany; Centre for Advanced

Studies in Nursing, Department of General Practice and Primary Care, University of Aberdeen, Aberdeen, UK; Quality of Life Research Center, Copenhagen, Denmark; Nordic School of Public Health, Gottenburg, Sweden, Scandinavian Institute of Quality of Working Life, Oslo, Norway; Centre for Quality of Life of the Hong Kong Institute of Asia-Pacific Studies and School of Social Work, Chinese University, Hong Kong.

22.6 Targets

Our focus is on research, international collaborations, clinical work, teaching and policy in health, disability and human development and to establish the NICHHD as a permanent institute at one of the residential care centers for persons with intellectual disability in Israel in order to conduct model research and together with the four university schools of public health/medicine in Israel establish a national master and doctoral program in disability and human development at the institute to secure the next generation of professionals working in this often non-prestigious/low-status field of work.

22.7 Contact

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