

THE AMERICAN JOURNAL OF PSYCHIATRY RESIDENTS' JOURNAL

February 2015

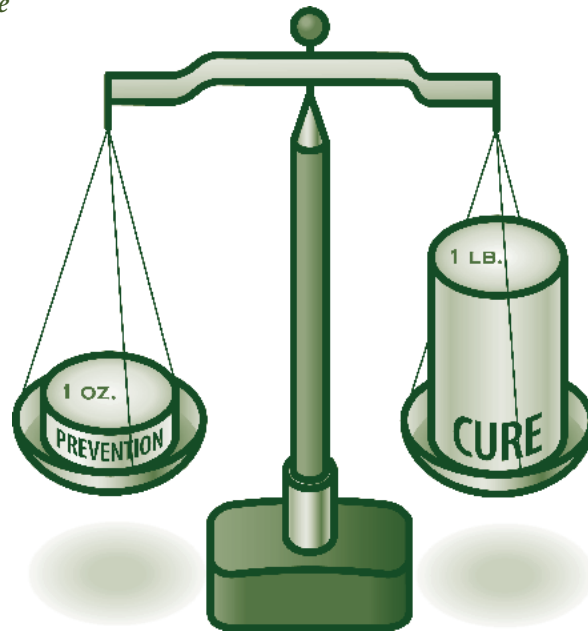
Volume 10

Issue 2

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In This Issue



This month's issue of the *Residents' Journal* focuses on the topic of prevention in psychiatry. In an editorial, Amritha Bhat, M.B.B.S., M.D., discusses the pursuit of mental well-being, including reducing risk factors, enhancing protective factors, and preventing recurrences and occurrences. In a review article, Adarsh S. Reddy, M.D., Ph.D., provides an overview of important concepts for effective secondary prevention of antipsychotic-induced hyperprolactinemia. Vivek Datta, M.D., M.P.H., explores the possibility of prevention of schizophrenia onset through the development of interventions for populations at ultra-high risk for psychosis. Joseph Siragusa, M.D., examines early neurobiological development modulating vulnerability to major psychiatric diseases at genomic, hormonal, and structural levels. Lorena E. Reyna, M.D., discusses early preventive interventions for child and adolescent depression. Rehan Puri, M.D., M.P.H., emphasizes the role of prevention strategies to counteract antisocial personality disorder. Lastly, Rebekah Nash, M.D., Ph.D., and Kristen N. Gardner, Pharm.D., present a case demonstrating the interaction between rifampin and clozapine and summarize the clinical implications of this interaction, demonstrating secondary prevention in psychiatry.

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Prevention in Psychiatry and the Pursuit of Mental Well-Being

Amritha Bhat, M.B.B.S., M.D.

It has been estimated that primary care physicians spend about 20% of their time on preventive services (1). Psychiatrists, on the other hand, spend the majority of their time treating and resolving crises and much less time on prevention. There are times when postoperative delirium can be prevented, as can recurrent episodes of a mood disorder. However, we have very little time and training to think about or practice prevention and the promotion of mental well-being. This is ironic, considering that in the most recent Global Burden of Disease Study, mental illness ranked highest for years lost to disability, at 22.9% (2). This does not include the effects on families, economic consequences of lowered productivity, and crime associated with mental disorders. As for the financial impact, costs associated with mental disorders can range as high as \$247 billion per year. Of course, preventing mental disorders is a challenging task. Risk factors for mental illness are omnipresent: poverty, malnutrition, poor access to education, and trauma. Successful preventive interventions therefore need to target multiple areas and be culturally relevant. This is why prevention must become the business not only of psychiatrists but also of policy makers.

A decade ago, a report from the Institute of Medicine (3) exhorted behavioral health to enable routine preventive interventions in schools and in community services. More recently, The National Prevention Strategy (4), part of the Affordable Care Act, prioritized mental health.

How does all of this translate into research work and clinical care? Not very well, unfortunately. Although the need to increase the evidence base for prevention in psychiatry is recognized, the gap between researchers and policy makers remains wide, probably because implementation of prevention research takes

The realistic goal is perhaps not a utopian complete absence of disease or stress but rather the ability to adapt or recover when adversity strikes.

several years, but policy makers have shorter timelines. For example, one of the most widely used substance use prevention programs, DARE (Drug Abuse Resistance Education), has been repeatedly shown not to work.

It is easy to get disheartened while working in a system that is overburdened and unable to reach many people who require treatment. Where, then, is there time or are there resources available to allocate to prevention? How can we prevent something when we do not know what causes it? We do know that improving nutrition, schooling, and social networks is protective, as is parenting education to foster secure attachment. We can encourage these primary preventive measures. Evidence-based secondary preventive interventions include collaborative care to prevent morbidity in the primary care population (5), early intervention programs for high-risk infants, psychotherapy for high-risk mother-infant dyads, and school-based cognitive-behavioral therapy for depressive symptoms (6). New research findings continue to emerge, several of which are summarized in the articles in this issue.

The realistic goal is perhaps not a utopian complete absence of disease or stress

but rather the ability to adapt or recover when adversity strikes and the realization of potential. We must broaden our focus to include coping skills *and* stressors, reduce risk factors *and* enhance protective factors, prevent recurrences *and* occurrences, and move from being reactive to being proactive. The articles in this issue can inform this paradigm shift.

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The author thanks Wayne Katon, M.D., for his guidance and mentorship.

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Secondary Prevention of Antipsychotic-Induced Hyperprolactinemia

Adarsh S. Reddy, M.D., Ph.D.

Antipsychotics are commonly associated with side effects such as extrapyramidal symptoms (rigidity, akathisia), tardive dyskinesia, and weight gain. The less commonly appreciated side effects are those related to antipsychotic-induced hyperprolactinemia. Several in-depth reviews about this topic are available. The present article provides an overview of essential concepts for the effective secondary prevention of antipsychotic-induced hyperprolactinemia that should be mastered by the psychiatry resident. This article differs from previous reviews on this topic in that it emphasizes pathophysiology and addresses future developments in the field. Essential references are provided for further in-depth discussion of clinical management.

Pathophysiology of Antipsychotic-Induced Hyperprolactinemia

Prolactin is a peptide hormone secreted by the lactotroph cells of the anterior pituitary gland. The secretion of prolactin by the pituitary is primarily regulated by dopamine. Traditionally, prolactin was thought to be secreted from the pituitary. However, more recently, autocrine and paracrine secretion have been demonstrated in several tissues, including of the breast, prostate, and liver (1). The secretion of prolactin is influenced by several physiological factors, including exercise, stress, sexual activity, pregnancy, and nursing. These physiological stimuli influence the tuberoinfundibular dopaminergic neurons in the hypothalamus. Several chemical mediators regulate the secretion of dopamine from the tuberoinfundibular dopaminergic neurons (Figure 1). The stimulation of the D₂ receptors on lactotroph cells inhibits the secretion of prolactin. Blockade of D₂ receptors by antipsychotics results in elevation of prolactin levels (2). The level of D₂ block-

ade necessary for antipsychotic effect is generally accepted to be approximately 80% in positron emission tomography (PET) studies (3); however, the correlation between D₂ blockade and prolactin elevation has not been studied, possibly because of limitations of PET resolution. Kapur et al. (4) showed that in rats, about 25% striatal D₂ blockade by olanzapine results in a prolactin level of 76 ng/mL, and about 10% striatal D₂ blockade by risperidone results in a prolactin level of 469 ng/mL. However, it is unclear whether these results could be directly extrapolated to humans.

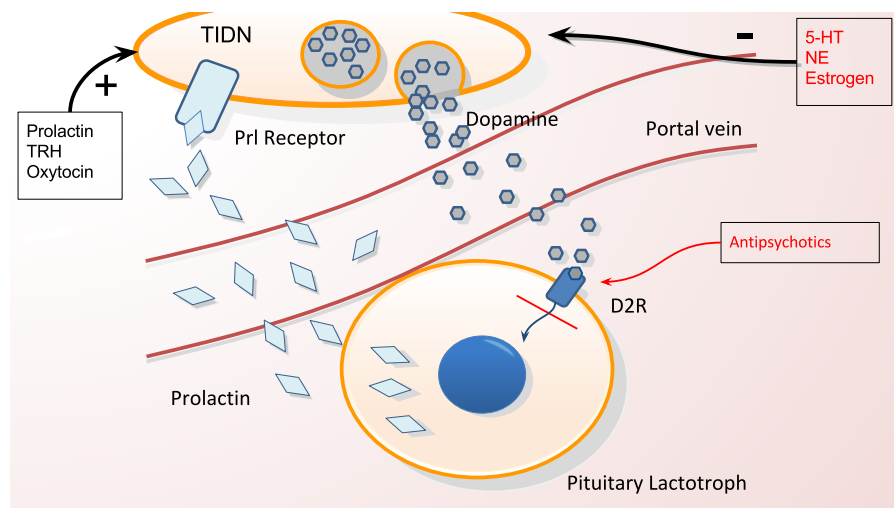
Antipsychotic-Induced Hyperprolactinemia in Clinical Practice

Prolactin elevation (defined as >29 ng/mL) is commonly observed in patients receiving antipsychotic treatment, with an estimated prevalence of about 50%

(5), and several studies have shown this to be more common in women compared with men (6). Prolactin elevations occur early in the course of treatment in a dose-dependent fashion and can persist without evidence for tolerance, even up to 15 years (5, 7). Antipsychotic-induced hyperprolactinemia can influence sexual function, fertility, and bone mineral density (2) (Table 1). These can become important concerns in patients who have been receiving chronic antipsychotic therapy. Hyperprolactinemia-related side effects have the potential to decrease compliance to antipsychotics. Yet, routine screening for clinical symptoms of hyperprolactinemia is not commonly practiced.

Several questions arise when a clinician treats a patient with symptoms of hyperprolactinemia. What are the common presenting/associated complaints? When do we need to check prolactin levels? What information should be provided to the patient? Some antipsychotics, such as risperidone, are known for their

FIGURE 1. Regulation of Prolactin Secretion^a



^a Dopamine is secreted by the neuronal endings of the tuberoinfundibular dopaminergic neurons (TIDN). This release is regulated by various physiological factors and is stimulated by prolactin (PrI), thyrotropin-releasing hormone (TRH), and oxytocin, among other chemical mediators. Secretion of dopamine by the TIDN is inhibited by 5-HT, norepinephrine (NE), and estrogen, among other chemical mediators. The secreted dopamine reaches the anterior pituitary lactotrophs through the pituitary portal vein. Stimulation of the D₂ receptors inhibits the secretion of prolactin. Antipsychotics induce hyperprolactinemia by blocking the D₂ receptors on the lactotrophs. Of note, the anterior pituitary lies outside the blood-brain barrier.

TABLE 1. Symptoms of Antipsychotic-Induced Hyperprolactinemia^a

Symptom	
In Women	In Men
Amenorrhea/oligomenorrhea	Erectile dysfunction
Decreased libido	Decreased libido
Infertility	Gynecomastia
Dyspareunia	Galactorrhea
Galactorrhea	Bone loss
Acne/hirsutism	
Bone loss	

^a There is unclear evidence for increased risk of pituitary tumors, breast cancer, pancreatic adenomas.

propensity for hyperprolactinemia potential at therapeutic doses. What is the mechanism of this differential effect? When faced with the problem of prolactin-related side effects, what options are available to the clinician?

In the study by Kinon et al. (5), the probability of menstrual abnormality was 0.5 at a prolactin level of 100 µg/L and 0.65 at a level of 150 µg/L. In the Schizophrenia Trial of Aripiprazole Study (8), patients had a mean prolactin level of approximately 43 mg/dL and were found to have moderate sexual dysfunction (ASEX rating of approximately 19/30) (8). Antipsychotics have been shown to be associated with osteopenia and osteoporosis (2), and there is an increased risk of hip fractures in patients receiving antipsychotic medication (9). Preclinical literature associates antipsychotic use and pituitary tumors, mammary adenocarcinomas, and pancreatic adenomas (2). However, the clinical literature is ambiguous (10, 11) about the possibility of pituitary tumors, given the high rate of incidentalomas. Prospective studies are essential to understand the true association. Chronic hyperprolactinemia is associated with increased risk of breast cancer (12), and antipsychotics are associated with a slight but statistically significant increase in breast cancer risk (13).

Management of Antipsychotic-Induced Hyperprolactinemia

Per APA guidelines (14), routine prolactin level measurement is not recommended. Measurement of baseline and periodic plasma levels is recommended if indicated by the patient's clinical history. However, baseline functional inquiry (before starting an antipsychotic) and annual inquiry is advised. Clinicians should probe for any antipsychotic-induced hyperprolactinemia symptoms (see Table 1). Functional inquiry is also recommended during follow-up visits during and after the antipsychotic dose adjustment. It must be noted that patients may not disclose sexual side effects unless specifically asked. The risks of menstrual disturbances, infertility, sexual dysfunction, and bone loss should be discussed. Patients should therefore be informed about the risks of chronic antipsychotic medications as they relate to hyperprolactinemia. The elevated cancer risk could be mentioned with acknowledgement that the evidence is limited. Potential options for management of antipsychotic-induced hyperprolactinemia are outlined below.

Antipsychotics

All antipsychotics do not have the same propensity to cause prolactin elevation, despite proportionate D₂ receptor blockade in the CNS (4). Kapur et al. (4) showed that the propensity of the antipsychotic to elevate prolactin is related to its ability to cross blood-brain barrier. The lesser the permeability, the greater the likelihood that the peripheral D₂ receptors in the pituitary are blocked relative to the striatal D₂ receptors, resulting in greater elevation of prolactin. Agents with good permeability and a lower propensity to produce antipsychotic-induced hyperprolactinemia include olanzapine and quetiapine. This effect differs from that of aripiprazole and clozapine, which have a prolactin-sparing effect due to their partial D₂ receptor agonist or lack of significant D₂ blockade at clinically effective doses (3).

When side effects are present, it might be worth revisiting the risk-benefit of the antipsychotic with the patient. One obvious approach may be to lower the antipsychotic daily dose during the maintenance phase of schizophrenia in patients with first-episode psychosis and in patients receiving multiple antipsychotics (14). In patients who have severe illness, history of multiple hospitalizations, suicidality, and propensity for violence, as well as a history of non-compliance, other possibilities include switching to aripiprazole or clozapine. Several studies have demonstrated the feasibility of this effect, and in-depth studies relating to medication switching strategies are available (e.g., reference 15). If compliance is a concern, depot injection of aripiprazole could be considered. Other alternatives include switching to olanzapine or quetiapine, which have lower prolactin-elevating potential compared with risperidone (4).

D₂ Receptor Agonists

Sometimes it may not be possible to consider an alternative medication. In such cases, D₂ receptor agonists (bromocriptine, pergolide, and cabergoline) could be considered. Although concurrent use of D₂ antagonist and agonist appears counterintuitive from a mechanistic point of view, cabergoline, at dosages of 0.125 mg/week to 1 mg/day, has been used to treat antipsychotic-induced hyperprolactinemia (e.g., reference 16). However, D₂ receptor agonists can precipitate mania and psychosis at dosages of 0.5 mg/day or more (17), and caution is warranted when using D₂ agonists. Mechanistically, concurrent use of D₂ receptor agonist and an antipsychotic would make sense only if the D₂ receptor agonist had low blood-brain barrier permeability. Carmoxirole is one such drug that has shown specific effects on prolactin decrease without a central effect in mice (18); however, it is not yet available clinically.

Novel/Investigational Treatments

Prolactin-receptor antagonists (e.g., Δ1-9-G129R-hPRL) that can inhibit the local actions of prolactin are also under active development (19). Estrogen supplements could be a potential option;

however, systematic evaluation has not been carried out thus far.

Conclusions

In conclusion, the clinician should be vigilant about the possibility of side effects related to antipsychotic-induced hyperprolactinemia. Although, higher prolactin elevation correlates with greater symptoms, it is difficult to predict the symptom severity with prolactin levels. Management should be largely based on symptom inquiry. The clinician should be aware of the options for the optimal management of side effects related to antipsychotic-induced hyperprolactinemia.

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The author thanks Dr. Nuri Farber for guidance and editorial support. The author also thanks Drs. Sandarsh Surya and Iffat Bhuiyan for their helpful comments in the writing of this manuscript.

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Prevention of Psychosis in Ultra-High-Risk Individuals

Vivek Datta, M.D., M.P.H.

Schizophrenia is a devastating psychiatric illness, with far-reaching consequences for sufferers, families, and society at large. In recent years, there has been a burgeoning research base on the genetics, epidemiology, and treatment of schizophrenia, which includes individuals deemed ultra-high risk for developing psychosis. With the cost related to schizophrenia estimated to be \$62.7 billion in 2002 in the United States alone and rising (1), and no true advances in the treatment of schizophrenia in 60 years, the possibility of prevention offers a glimmer of hope in a sea of therapeutic pessimism.

Schizophrenia is a complex genetic disorder believed to be the end-point of the confluence of genetic, environmental, and stochastic factors. However, a family history of schizophrenia is the greatest risk factor for the development of the disorder (2). Family history of schizophrenia is an infrequent exposure in the general population, meaning that the population attributable risk is only 5.5% (3). That is to say, if we could prevent all cases of schizophrenia related to family history, we would only prevent 5.5% of all schizophrenia cases. As such, targeting environmental exposures that may contribute less to the risk of developing schizophrenia but are more prevalent in the population may afford the best possibility for prevention. A number of environmental risk factors for schizophrenia have been identified. Of these, obstetric complications (4) and heavy cannabis use in adolescence (5) provide the most practical opportunities for intervention and are the focus of the present review.

In the clinical arena, the development of interventions for those at ultra-high risk for psychosis may offer the opportunity to prevent the onset of schizophrenia. A number of pharmacological and psychotherapeutic interventions have been evaluated that may bear some promise in preventing transition to schizophrenia.

Obstetric Complications

The association of obstetric complications with the risk of schizophrenia has been well replicated (4). Obstetric complications are common in the general population and confer a two-fold risk in the development of schizophrenia. Women with severe psychiatric illness are even more likely to experience obstetric complications, and thus their offspring have an increased risk of schizophrenia through both genetic and environmental exposures (6). Hypoxic injury in particular appears to confer increased risk of schizophrenia. Improved perinatal care for women in general, and women with severe mental illness in particular, may be a fruitful avenue toward preventing schizophrenia. In one cohort study, the population attributable risk of perinatal brain injury was 7% in the general population, with 86% of schizophrenia cases among survivors of perinatal brain injury attributable to the injury (6).

If obstetric complications have a causal role in the development of schizophrenia, then interventions to improve prenatal care may prevent some cases. We might also expect a decline in the incidence of schizophrenia with improvements in obstetric care in recent years. Findings in this respect are equivocal and confounded by changes in the prevalence of other environmental risks. Thus far, no interventions aimed at improving obstetric care for schizophrenia prevention have been systematically studied.

Warner (7) suggested that improvements in prenatal care in general be targeted in developing countries, whereas efforts in developed countries should be focused on improving prenatal care in women with schizophrenia. He further suggested interdisciplinary study of this issue and provision of educational information, not only for women with schizophrenia but for psychiatric, obstetric, and primary care providers in order to improve out-

comes. This should be supported with the goal of eliminating inequalities in prenatal care alone; however, it is unclear how successful such an intervention would be in reducing obstetric complications, let alone preventing cases of schizophrenia. Given the economic burden of schizophrenia, Warner estimated that a program costing \$2.5 million would pay for itself if it only prevented three cases of schizophrenia. To date, no national guidelines exist on perinatal care in women with schizophrenia, nor have any interventions to improve such care been evaluated.

Cannabis Use in Adolescence

Several cohort studies show an association between heavy cannabis use before the age of 18 and the development of schizophrenia (5). The population attributable risk has been estimated to be between 8% and 14% (8). Although the association between cannabis and schizophrenia is controversial, there is good reason to believe that there is a causal link. In one case-control study, psychosis was associated with higher potency cannabis (in terms of delta 9-tetrahydrocannabinol [THC] content) and more chronic use, suggesting a dose-dependent effect (9). The effects of THC on mesolimbic dopamine release are in keeping with the dopamine hypothesis of schizophrenia (2). Genetic studies have found that the *AKT1* rs2494732 single-nucleotide polymorphism may mediate risk of psychosis with cannabis use (10). These findings are subsequent to failed replication of the Val58Met polymorphism of *COMT* and cannabis interaction in psychosis.

There is no evidence that legislation significantly affects cannabis use, and marijuana is becoming legal in more territories. Educational interventions aimed at young people, schools, and physicians could help young people better evaluate the risks of heavy cannabis use and potentially reduce the risks. Marijuana is often regarded as

benign, but as many as 9% of users are believed to meet criteria for cannabis use disorder (11). Recognition of cannabis use disorder in adolescents and effective treatment may also play a role in preventing cases of schizophrenia. The identification of genetic polymorphisms that mediate the risk of cannabis use may provide the opportunity for personalization of education and prevention strategies. The role of educational programs regarding marijuana use and the effects of treating adolescent cannabis use disorder on subsequent development of psychosis deserves further study.

Interventions for Prodromal Psychosis

Individuals experiencing attenuated psychotic symptoms, brief limited intermittent psychotic symptoms, or deteriorating functioning with a genetic loading for schizophrenia have been deemed ultra-high-risk individuals (12). A number of interventions have been assessed that show initial promise but require further investigation.

Cognitive-Behavioral Therapy (CBT)

CBT for schizophrenia is a well-established intervention as an adjunct to antipsychotic medication and has also been used alone. CBT has been investigated in the ultra-high-risk population and appears to be preferred over antipsychotics (13). In a meta-analysis of seven randomized controlled trials of CBT compared with usual care or nonspecific therapy in psychosis prevention, there was a 50% reduction in the development of psychosis at 6, 12, and 18–24 months following CBT (14). In one randomized controlled trial of CBT compared with supportive psychotherapy, there was no significant difference in transition to psychosis between the interventions, although CBT appeared to have more rapid effects (15). Although supportive psychotherapy is often used as a control intervention believed to be inert, it is clear that even supportive psychotherapy may have utility in both prodromal and frank psychosis and warrants study in itself.

Antipsychotics

To date, low-dose olanzapine, risperidone, and aripiprazole have been investigated in prodromal psychosis. A randomized controlled trial of 115 ultra-high-risk participants comparing CBT plus risperidone with CBT plus placebo and supportive psychotherapy plus placebo found no difference of statistical significance between the treatment groups (15). There did appear to be a reduction in transition to psychosis in all three treatment arms, highlighting the potential for supportive psychotherapy to be a useful intervention in preventing psychosis. In a small double-blind randomized controlled trial (N=60) comparing olanzapine with placebo in prodromal psychosis, results favoring olanzapine in preventing transition to psychosis nearly reached statistical significance (16). The small sample size may mean that the study was underpowered to determine an effect. Further studies are therefore warranted, but antipsychotics cannot be recommended in prodromal psychosis based on these findings. An open-label study of aripiprazole in prodromal psychosis with 15 participants showed initial promise (17). A study of aripiprazole compared with CBT compared with clinical management plus placebo is under way, but the findings are yet to be reported (18). In summary, antipsychotics cannot be positively recommended in the prevention of psychosis.

Omega-3 Fatty Acids

In a 12-week randomized controlled trial comparing 1.2 g/day of omega-3 fatty acids with placebo over a 40-week follow-up period among 81 individuals deemed to be ultra-high risk, 4.9% of those receiving omega-3 fatty acids compared with 27.5% receiving placebo transitioned to psychosis at 12 months ($p=0.007$) (18). The number needed to treat to prevent one individual developing psychosis was 4. Larger replication studies are needed.

Discussion

Interventions aimed at preventing obstetric complications and reducing inequalities in prenatal care in women with

severe mental illness could potentially prevent some cases of schizophrenia. Education of clinicians and young people about the association between cannabis use and psychosis, and genetic risk stratification for cannabis use and psychosis, could potentially be effective in preventing other cases. Treatment of cannabis use disorder in adolescence should be investigated with regard to the potential to prevent the development of psychosis. While antipsychotics thus far have shown no significant advantage in preventing psychosis, both CBT and supportive psychotherapy hold promise in preventing up to 50% of those identified as ultra-high-risk individuals from transitioning to psychosis. Furthermore, omega-3 fatty acids are a low-cost, low-risk intervention showing early promise in preventing psychosis.

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Early Intervention: The Developing Brain and Psychiatric Disease

Joseph Siragusa, M.D.

Effective prevention of any multifactorial disease invariably involves some combination of sociopolitical shifting, reallocation of resources, and changes in policy. However, the overwhelming public concern that seems prerequisite for such change is always driven through dissemination of knowledge (i.e., education). In order to start thinking about psychiatric disease as a preventable entity, it will be helpful to summarize and review what we know in particular domains. The present article provides an overview of some neurobiological evidence in order to highlight opportunities for environmental and/or public health interventions that may mitigate some of the identifiable risk of psychiatric illness and outlines how intervening at the level of epigenetics may be a promising way to prevent psychiatric disease in the future.

Schizophrenia

Perhaps more than any other disorder, it is by now well accepted that schizophrenia is a condition in which genetic predispositions are influenced by environmental factors. A recent landmark genome-wide association study found that groups of interacting gene clusters are associated with a finite number of schizophrenia endophenotypes (1). As the underlying genetics for this disease becomes more precisely delineated, the fact still remains that 60% of patients diagnosed with schizophrenia have unaffected first-degree relatives, and there is only about a 60% concordance rate of schizophrenia among monozygotic twins (2, 3). Clearly, genetic advances can only bring us so far in understanding the etiology of this disease, and there is significant room for environmental influence on disease manifestation.

There is a growing body of evidence showing that early brain insults occurring prenatally and during adolescent

neurodevelopment lead to susceptibility to schizophrenia. Research has shown that gestational exposure to infection is a significant risk factor for schizophrenia. Infections such as cytomegalovirus and toxoplasmosis often compromise fetal neurodevelopment and lead to delayed development and hypoplasia of certain brain regions (4). Two studies have shown that primary maternal infection with *T. gondii* early in gestation confers at least a two-fold risk for schizophrenia (5). An even greater risk was demonstrated in cases of exposure to influenza during the first half of gestation (6). The pathophysiology may not be a result of the infectious agents themselves but rather the result of exposure to mediators of inflammation, such as cytokines, that disrupt the maturation of oligodendrocytes and other types of neurons critical to neurodevelopment (7). The idea that perturbations of the immune system can lead to neuropsychiatric consequences is not new. Systemic infections, such as Lyme disease, and rheumatological disorders, such as systemic lupus erythematosus, can lead to debilitating psychosis. The relatively new field of immunopsychiatry is already drawing connections at the molecular level between immunology and psychiatry.

Several studies have linked childhood trauma (e.g., sexual/physical abuse, loss of parent) not only to the development of psychotic disorders but also to the severity of positive symptoms (8). Animal studies corroborate this link by showing how early stressors result in subcortical dopamine hyperresponsivity (9). Additionally, early trauma is also associated with hyperresponsivity of the hypothalamic-pituitary-adrenal (HPA) axis in adulthood. One interesting prospective cohort study followed offspring conceived around the time of the 6-day Arab-Israeli War in 1967 and found

higher incidence of schizophrenia in offspring whose second gestational month correlated with the pugilistic exposure (10). Indeed, there is overwhelming evidence that neuroendocrine dysregulation may contribute to the etiology of psychotic illness. Alterations in the HPA axis lead to disruption of neurophysiologic “set points,” resulting in future behavioral problems (11). These alterations are thought to exert their effects epigenetically in ways such as changing patterns of methylation at CpG islands or through histone modification. Additional support for extra-genetic influence is the association between advanced paternal age and elevated risk for schizophrenia, which is likely conferred through increased length of time for mutations to occur (12).

Much attention has also been given to structural brain abnormalities in schizophrenia. For example, an upward bowing of the corpus callosum has been suggested to be a neuroanatomical marker in individuals possessing biological vulnerabilities for schizophrenia (13). Additionally, initial cortical gray matter deficits have been identified in certain prefrontal and parietal regions of individuals with childhood-onset schizophrenia. Interestingly, healthy siblings of childhood onset schizophrenia probands show very similar neuroanatomic deficits early in adolescence. However, in healthy siblings, there seems to be a profound improvement or restitution of these deficits by young adulthood (14). This has led to the suggestion that some endophenotypes of schizophrenia follow a pattern reflective of a progressive neurodevelopmental disorder. Gaining insight into neurodevelopmental trajectories may lead to the identification of highly vulnerable periods in which particular environmental factors exert their influence. Questions such as whether there are points at which

trajectories can be identified and reversed have yet to be answered.

Depressive Disorders

The etiology of major depression is likely multifactorial, resulting from environmental influences on neurophysiological processes. Recent attention has been given to the role of immunology in major depression. Indeed, depressed patients have been found to have elevated levels of proinflammatory cytokines, acute-phase reactants, chemokines, and cellular adhesion molecules (15). In one prospective study of older subjects with no previous psychiatric history, elevated inflammatory biomarkers were found to precede the onset of depression (16). Interestingly, the link between inflammation and depression may account for the 5- to 10-fold greater prevalence of depression in patients with purely medical illness (17). At the genetic level, allelic variants of genes for interleukin-1 beta and tumor necrosis factor alpha are associated with increased risk for depression and reduced responsiveness to antidepressants (18). Further supporting this connection, many patients being treated with antagonists of tumor necrosis factor alpha have reported reduction of depressive symptoms prior to symptomatic improvement of their medical conditions (19).

One potentially causative link between psychosocial stress and the development of depression is that psychological stress promotes an increase in proinflammatory mediators. In fact, this connection has been well demonstrated in animal models. For example, social isolation in rats has been found to inhibit the expression of brain-derived neural growth factor in the hippocampus (20). This suggests that the immune system may even play a role in synaptic plasticity. Furthermore, inflammatory cytokines have been found to upregulate hormones involved in the HPA axis. Given that hyperactivity of the HPA axis and the sympathetic nervous system is involved in the pathophysiology of depression, the role of the immune system in mitigating HPA responsivity may offer interventions further upstream in the disease process.

Research has shown that development and responsivity of the HPA axis begins in the prenatal environment. Prenatal exposure to maternal mood symptoms confers increased susceptibility to behavioral disturbances in childhood and throughout life. Biochemically, this manifests as abnormalities such as elevated cortisol levels and lower levels of serotonin in early life (21). Interestingly, animal models have shown that early exposure to stress correlates with a reduction in hippocampal glucocorticoid receptor expression. In one human study, this effect was shown to be mediated by hypermethylation of specific regions in the glucocorticoid receptor gene (*NR3C1*) (22). If altered HPA stress reactivity begins epigenetically in the prenatal environment, this could also be a potential target for prevention of mood disorders through psychosocial interventions before and during early pregnancy. This could be as simple as promoting meditation and mindfulness to mothers during these periods.

Even maternal diet has been shown to significantly affect temperamental set points. One study using a nonhuman primate model found a correlation between maternal high-fat diet and dysregulation of the serotonergic system in fetal offspring (23). Behaviorally, this manifested as increased aggression and anxiety in response to threatening novel objects. Here again, the pathophysiology is thought to be related to high levels of inflammatory markers induced by lipotoxicity. Considering the high-fat content of the typical American diet, improving maternal nutrition provides a ready target for very early prevention of behavioral disorders.

A recent longitudinal study of 86 adolescents followed volumetric changes in certain areas of the brain from early to mid-adolescence. In participants diagnosed with depressive disorder, attenuated changes in hippocampal and putamen volume were observed (24). Similar to the conceptualization of schizophrenia as a neurodevelopmental disorder, this suggests that trajectory of growth in certain brain regions may represent endophenotypes of depression. It is likely that structural vulnerabilities are influenced by factors in the early childhood environ-

ment to drive particular trajectories of neurodevelopment.

Implications for Preventive Psychiatry

Our enhanced understanding of the etiologies of mood and psychotic disorders from genetic, hormonal, and structural viewpoints may permit earlier intervention and even prevention. As the complexity of the gene-environment interaction becomes untangled, we are beginning to see how we can alter the onset and course of psychiatric disease. Proof of concept is already under way for many connections between immunological factors and psychiatric pathology. In the future, novel treatments and therapies will allow us to intervene earlier in the disease process.

The growing body of scientific data should reassure policy makers that changes at the level of public health may, in the future, have considerable impact on the prevention of mental illness. Much like rudimentary improvements in sanitation led to significant reduction of infectious disease in the early 20th century, there may be simple measures that can be taken to mitigate the burden of psychiatric illness. These include providing more comprehensive, widespread prenatal and antenatal care and educating mothers on both stress reduction and diet modification during pregnancy. Given the clear reciprocity between mental and physical health, adding psychiatry to the paradigm shift of preventative care will be of utmost importance.

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The author thanks Dr. Srinivasa Gorle and Jonathan Swinden for their assistance with this article.

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Early Preventive Interventions for Child and Adolescent Depression

Lorena E. Reyna, M.D.

Identifying and treating depression in children and adolescents is important, both for the ongoing development of the child and potentially for adult outcomes. However, only 20% of youths with depression are identified and receive adequate treatment (1). Consequences of depression include difficulty with relationships, impaired school and work performance, and increased risk for substance abuse and suicide (2). It is interesting to note that one-half of all lifetime cases of mental disorders begin by age 14 (1). Additionally, about 20% of adolescents have a depressive episode before age 18 (3). Of these adolescents, about 20% develop recurrent, persistent, and chronic depression that may be difficult to treat (2). In addition to early identification of individuals with depression, there is a need for interventions to prevent depression. Clearly, preventive measures that target children and adolescents have the potential to help in the prevention of life-long illness.

The present article reviews risk factors and protective factors associated with psychopathology and examines different levels of intervention that illustrate approaches to the prevention of depression.

Risk and Protective Factors

There are numerous risk factors that are associated with the development of psychopathology. Protective factors, in turn, help reduce the risk. The presence of multiple risk factors and the lack of protective factors predispose a child to develop a mental health disorder (Table 1). Preventive interventions seek to counteract risk factors and help increase or promote protective factors (4).

Types of Preventive Interventions

There are three main forms of preventive interventions (4–6), as described below.

Universal Interventions

Universal interventions target the population as a whole. They are positive and proactive. These interventions are applied regardless of individual risk status and tend to be the easiest to adopt because of the low stigmatization of participants. School-based programs that focus on improving cognitive, problem-solving, and social skills strengthen protective factors. Other examples include programs that promote wellness and that seek to reduce child abuse/neglect and bullying.

Selective Interventions

Selective interventions target individuals whose risk of developing a mental disorder is higher than average. Examples of such interventions include teaching behavioral child rearing strategies to parents of children with conduct problems, implementing programs for children that teach coping with major life events (death of a parent or divorce), and incorporating family-based interventions for children with a parent with a mental health disorder.

Indicated Interventions

Indicated interventions target individuals who have prodromal signs or symptoms of a mental health disorder but do not meet diagnostic criteria. Cognitive-behavioral prevention programs for youths with depressive symptoms and evidence-based anxiety prevention programs have proven beneficial.

Universal Interventions: Health Education in Elementary Schools

It is common for health education curricula to incorporate a universal intervention approach for the prevention of mental health disorders. Evidence suggests that a greater impact may be achieved if health education targets multiple risk factors during the elementary years (7). One meta-analysis examined 53 randomized controlled trials of psychological and educational programs for the prevention of depression (8). About one-half of these programs were universal interventions. Most of the programs

TABLE 1. Risk and Protective Factors in the Development of Psychopathology^a

Risk Factors	Protective Factors
Perinatal complications	Empowerment
Organic handicaps, sensory disabilities	Social support and community networks
Lack of housing, transportation, education	Social support of family and friends
Access to drugs and alcohol	Positive interpersonal interactions
Attentional deficits	Ability to cope with stress and face adversity
Exposure to violence and trauma	Adaptability and autonomy
Apathy or emotional blunting	Early cognitive stimulation
Emotional immaturity	Exercise
Low self-esteem	Self-esteem
Emotional dysregulation	Good parenting
Poverty	Positive attachment and early bonding
Parental mental illness and substance abuse	Positive parent-child interaction
Child abuse and neglect	Problem-solving skills
Stressful life events	Socioemotional growth
Family conflict	Stress management
Poor bonding to parents	Prosocial behavior
Peer rejection, alienation, and isolation	Literacy
Scholastic demoralization and school failure	Skills for life
Racial injustice and discrimination	Social and conflict managing skills

^a For further details, see data provided by the World Health Organization (4) and Greenberg et al. (5).

focused on incorporating components of cognitive-behavioral therapy, while others focused on self-efficacy, stress reduction, trauma coping strategies, or optimism. The results of this meta-analysis showed that compared with no intervention, universal depression prevention programs reduced depressive symptoms up to 3 to 9 months postintervention. However, the effect sizes were small, the studies had a high degree of heterogeneity, and there was a lack of placebo or attention comparison groups. Additionally, when compared with active interventions, universal interventions have not demonstrated statistical significance (8, 9).

There are many prevention programs available. The Michigan Model for Health is a comprehensive prevention approach curriculum. Students receive a total of 25 lessons through grades 4 and 5 that focus on social and emotional health, alcohol, tobacco, safety, nutrition, and physical activity. One study found that students who participated in the Michigan Model for Health had better social and emotional skills, interpersonal skills, and drug-refusal skills (7). They also exhibited lower levels of aggression and drug use intentions (7, 10). Although these are promising results, only teacher self-reports were used to measure the degree of fidelity in implementing the curriculum, and there was differential exposure to the curriculum for the intervention and control groups. Schools are promising sites for the delivery of universal interventions, and while small studies have shown promise, the effects have not been replicated in large trials conducted in everyday settings (9).

Selective Interventions: Family Factors

Selective and indicated interventions have shown to be more effective than universal interventions. A meta-analysis conducted by Horowitz and Garber (11) assessed the efficacy of 30 prevention interventions. Selective interventions showed small to moderate effect sizes in the reduction of depressive symptoms. One study assessed targeted children of divorced parents and provided divorce education and problem-solving skills training and encouraged

emotional expression during eight weekly group sessions. While this study showed a large postintervention effect size, it did not produce an effect size at 6 months of follow-up. Another intervention assessed was one that used a modified version of the Penn Resiliency Program, which targeted low-income Latino children. This study focused on problems specific to low-income families and provided skills for managing interpersonal conflict. Information was provided over 12 weekly 90-minute group sessions. This approach resulted in the reduction of depressive symptoms even after 6 months postintervention (11). However, the study involved a small sample size, and results need to be replicated in larger trials to classify this approach as a successful selective intervention.

Approximately one in five Americans will develop depression in their lifetime. As such, there are many children living at home with a depressed parent, and 61% of these children will develop a psychiatric disorder by their adolescent years (12, 13). Beardslee et al. (14) developed a family-based preventive intervention strategy that targets nondepressed youths (ages 8–15 years) who have depressed parents. Families were assigned to a lecture- or clinician-facilitated intervention. Parents were encouraged to help their children build resilience by promoting healthy friendships and success outside of the home and by increasing their understanding of parental illness and of themselves. Parents in both groups reported change in child-related behaviors and attitudes, with greater change reported in the clinician-facilitated group (mean number of changes: 9.8 compared with 6.3, respectively). Furthermore, changes were still evident 2.5 years postintervention. By helping children understand parental illness, there is a promotion of resiliency (15). Thus, taking a family-based approach can lead to the reduction of depressive symptoms.

Indicated Interventions: Cognitive-Behavioral Prevention Programs

A more recent meta-analysis conducted by Stice et al. (16) evaluated 32 prevention

programs (including universal, selective, and indicated). From these programs, 41% produced a significant reduction in depressive symptoms (small effect size), and 13% significantly reduced the risk for future onset of major depression. An important finding of this meta-analysis is that indicated programs were more likely to prevent future onset of major depression. For example, one study sought to determine whether a group cognitive-behavioral prevention program prevented the onset of depression in adolescents (2). Adolescents in this study had current subsyndromal depressive symptoms, past history of major depressive disorder, or both. They also had at least one caretaker who had a history of a major depressive episode. The program consisted of eight weekly, 90-minute group sessions followed by six monthly continuation sessions or usual care alone. The findings of this study showed that episodes were 11% lower in the cognitive-behavioral prevention program. A second study examined the efficacy of a shortened version of a cognitive treatment program targeting adolescents with subsyndromal symptoms and depressed parents. The participants were taught cognitive restructuring techniques and participated in 15 sessions of group cognitive therapy. This study showed a cumulative major depression incidence rate of 9.3% for group cognitive therapy compared with 28.8% for usual care alone through a mean 15-month follow-up (17).

Conclusions

Prevention approaches that have produced statistically significant effects share certain similarities. The studies reviewed in the present article targeted high-risk individuals, were of shorter duration, incorporated homework assignments, were delivered by professionals, and sampled more females and older adolescents (16). Females have higher incidence of depression, and the risk for depression increases in older adolescence, thus likely counting for the effects noted. Additionally, most studies assessed the reduction of depressive symptoms and not the reduction in the incidence of depression. Therefore, most available programs should be thought of as early-intervention strate-

gies rather than primary prevention until further assessment of these programs can be made. Most of the prevention programs produced small effects in the reduction of depressive symptoms, and it is essential that new or updated programs incorporate elements of the most promising programs.

Furthermore, programs should be cost-effective, reproducible, and easily applied in diverse conditions. For children and adolescents who have multiple risk factors for depression, selective and indicated preventive interventions are more likely to show positive results. Depression is a debilitating disease, and by focusing on children and adolescents with risk factors, we can prevent life-long illness in many individuals.

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The author thanks Dr. Graham Emslie for guidance in the writing of this article.

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Strategies to Prevent Development of Antisocial Personality Disorder

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Because of the recent epidemic of violence in the United States, the Office of the U.S. Surgeon General has called on the medical community to examine prevention strategies that can reduce the development of antisocial personality disorder in youths (1). It is estimated that nearly 500,000 fatalities occur annually as a direct result of injury from an individual with antisocial personality disorder (2). Additionally, the average economic toll on society by an antisocial personality disorder patient is 10-fold that of an unaffected individual (1). Antisocial personality disorder is highly resistant to both behavioral and pharmacological treatment (3). However, research has found that the disorder is preventable in children and adolescents (1). The present review discusses risk factors, screening tools, and prevention strategies described in the literature in order to educate physicians to identify patients at risk for developing antisocial personality disorder and to implement an intervention program.

Antisocial personality disorder debilitates the patient, disrupts the society, and causes great economic damage resulting from the high costs associated with delinquent acts (2, 4, 5). Other costs are intangible, for example, the psychological pain and suffering inflicted upon victims and family members (2).

Prevention refers to treatment interventions initiated before the onset of a disorder and is highly appropriate for antisocial personality disorder (6). Antisocial behaviors begin in childhood and peak in late adolescence, with 10%–33% of children with antisocial behaviors going on to develop antisocial personality disorder as adults (1). By adulthood, antisocial personality disorder becomes a solidified part of the patient's personality and is no longer amenable to treatment (3). With widespread practice of preven-

tion strategies, it is possible to limit the disease burden placed on patients and society.

Risk Factors

Individuals can be at risk for the development of antisocial behaviors starting from the prenatal period all the way through the adolescent years (7). Nonmodifiable risk factors, such as genetic predisposition, play a limited role in prevention. However, awareness of subtle modifiable risk factors, such as poor academic performance, bullying at school, and various environmental influences, is important in order to implement timely prevention strategies.

In a study of children and adolescents up to age 14, Tremblay et al. (8) found that poor school performance is a major correlate of future antisocial behavior. Compromised cognitive functioning at an earlier age has been shown to lead to antisocial behavior by age 17. However, it is unclear whether poor academic performance is entirely due to low IQ or influenced by factors such as the school environment or the teacher's personal attitudes and skills (9). Regardless, poor academic performance raises concerns regarding the development of antisocial personality disorder.

Bullying exists in different forms. It can be either verbal or physical. Physical bullying is a key predictor of antisocial development. Although antibullying programs have shown to decrease victimization, the exact benefit has yet to be determined (10).

Several environmental factors contribute to the development of antisocial personality disorder, some starting as early as the prenatal stage. For example, parental characteristics such as lack of education, young maternal age, and being a single parent make children more vulnerable to

developing the disorder. Peer and societal influences are also contributing factors, since there is a direct correlation between residing in an adverse neighborhood and participation in criminal activities. Furthermore, exposure to domestic violence, physical abuse, and substance abuse can contribute to the development of antisocial personality disorder (7).

Screening

Early detection of symptoms can be supportive in prevention. Thus, being familiar with the diagnostic criteria for antisocial personality disorder is essential. An overview of DSM-5 criteria for antisocial personality disorder (categorized as a cluster B personality disorder) is presented in Table 1 (11).

Since children are reluctant to report their own delinquent behaviors, as well as those of their peers, a detailed psychosocial evaluation is essential in the screening process. The data collected by health care professionals and the information provided by teachers and parents are key factors in early detection.

Child health professionals have access to children's medical history, which can be utilized to assess longitudinal changes in patient behavior. A nationwide study in the Netherlands, in which child health professionals assessed primary school-aged children's behaviors throughout their development, demonstrated that behaviors such as fighting, stealing, and setting fires were early alarming signs that predisposed children to antisocial personality disorder.

The Antisocial Process Screening Device is a 24-item survey that can be easily completed by teachers and parents to detect the early onset of antisocial personality disorder (12, 13). The Antisocial Process Screening Device is a multidimensional scale, which is able to screen

TABLE 1. Diagnostic Criteria for Antisocial Personality Disorder^a

Criteria
Indifference of the rights of others since age 15, with three out of seven of the following traits:
• Disregard for the law and norms of the society.
• Deceitful and involvement in theft.
• Impulsive and lack of insight to the consequences of ones actions.
• Physical aggression and aggravation.
• Unconcerned for the safety of oneself and others.
• Negligence.
• Absence of repentance.
Age ≥18
Evidence of conduct disorder with onset prior to age 15
Antisocial behavior not influenced by underlying schizophrenia or bipolar disorder

^a For further details on the diagnosis of antisocial personality disorder, see DSM-5 (11).

for characteristic patterns of antisocial behavior in children from ages 6 to 13 years. The Youth Psychopathic Traits Inventory-Short Version is an accurate self-report measure of antisocial behaviors (14). Higher scores suggest that the individual is more likely to have conduct problems.

Interventions

In a selective review, Bor et al. (6) demonstrated a logical strategy intervention in the development of antisocial personality disorder, based on the developmental age of the patient.

Prenatal to Age 2

When an expecting mother with risk factors for raising children with antisocial personality disorder is identified, it is possible to administer an intervention immediately. In a controlled trial, the University of Rochester Nurse Home Visitation Program found that providing high-risk mothers with education-based nursing home visits up to age 2 of the child resulted in up to a 50% decrease in delinquent behavior in the lifetime of the child (6). Research shows a causal relationship between delivery complications and the development of antisocial personality disorder (7). According to these results, at-risk pregnant mothers can be provided access to prenatal health care and personalized child development education as prevention measures.

Ages 3–10

Research on prevention strategies for at-risk children between the ages of 3 and 10 has shown the importance of education for both the parents and the child (15). Scott et al. (1) found that providing parents of high-risk children with the Incredible Years BASIC videotape program significantly decreased delinquent behaviors in the children, as demonstrated when they were followed up as adolescents. The Conduct Problems Prevention Research Group found that in addition to parental education, providing high-risk children in the first grade with a curriculum that promoted emotional understanding (Fast Track) also led to a significant decrease in high-risk behavior (6). The Early Risers Effectiveness Study reaffirmed the hypothesis that increasing literacy and emotional intelligence, as well as promoting parental disciplining, limits future antisocial behavior in this age group (8).

Ages 11–18

The two most effective forms of therapies available to adolescents and youths (11–18 years old) with antisocial behaviors are functional family therapy and multisystemic therapy (6). Experimental social development curricula have also shown success in preventing high-risk behaviors in adolescents in urban environments (16).

Functional family therapy is short-term family-based therapy, which treats both the family and the youth, encouraging them to identify negative emotions while focusing on long-term behavioral changes to address these emotions (17). Multisystemic therapy, on the other hand, focuses on factors in the youth's environment that negatively reinforce delinquent behavior and seeks to break off these associations. Both methods are effective, and the adolescent's particular situation should be considered when choosing either form of therapy (6).

Flay et al. (17) developed an experimental curriculum that taught social skills to adolescents in urban Chicago schools. These skills, which were hypothesized to counteract antisocial behavior, included empathy, refusal skills, and establishing role models. Higher-risk youths were given targeted interventions, such as safe sex and violence education, and they were provided group therapy sessions with their parents. This program was widely successful, reducing antisocial behavior up to 65% in this age group, albeit only in boys. In addition to providing all high-risk adolescents with either functional family therapy or multisystemic therapy, boys might also benefit from learning coping mechanisms.

Conclusions

From the available literature, one can glean that antisocial personality disorder is a pervasive disorder with a strong environmental etiology. Preventive measures to stop the progression of antisocial personality disorder in children and adolescents involve modifying the environment. Fortunately, at all stages of development, environmental factors such as parental education can be successfully modified with ameliorating results. From a review of the literature, one could argue that an individual with antisocial personality disorder is a product of failed childhood development. Thus, the role of the physician in the prevention of the disorder becomes clear, which is to identify children and adolescents who are at risk for developing antisocial personality disorder and to intervene by modifying their negative environmental perceptions and exposure.

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The author thanks Drs. Taimur Mian and Tahira Akbar, research fellows at Bergen Regional Medical Center.

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The Destabilizing Impact of Rifampin on a Patient Treated With Clozapine

Rebekah Nash, M.D., Ph.D.
Kristen N. Gardner, Pharm.D.

Clozapine often serves as the drug of last resort for treatment-resistant psychotic disorders. However, its efficacy can be severely compromised if its metabolism is increased by other medications. For example, clozapine is a substrate of several cytochrome P450 (CYP) enzymes, including CYP1A2 (primarily) and CYP3A4, CYP2C19, and CYP2D6, as well as P-glycoprotein (1–3). Rifampin is a potent inducer of several CYP450 enzymes, including CYP3A4 and members of the CYP1 and CYP2 families, as well as P-glycoproteins (4, 5). As a result, concomitant rifampin treatment increases the rate of clozapine metabolism, producing subtherapeutic clozapine concentrations and putting the patient at risk for clinical decompensation (3, 5).

While rifampin is known to affect clozapine metabolism, the extent to which, and the timeline over which, clozapine metabolism is affected by rifampin administration is poorly described. Only two previous case reports, to our knowledge, have documented this drug-drug interaction (6, 7). In the present report, we detail the changes in clozapine plasma levels, symptom severity, and the level of function prior to and following therapy with rifampin in a patient with schizoaffective disorder previously well-controlled on clozapine. We then discuss the adjustments in clozapine dosing required to restabilize the patient.

Case

“Mr. A” is a 44-year-old Caucasian man with a history of schizoaffective disorder and obsessive-compulsive disorder. He presented to the emergency department after demonstrating several days of unusual behavior, delusions, and increasing paranoia, all of which were a distinct departure from his baseline. His medications at the time of admission included

clozapine (350 mg/day), divalproex sodium extended-release (1,500 mg at bedtime), metoprolol succinate (100 mg every evening), rifampin (600 mg/day), and sertraline (200 mg/day). The patient denied use of over-the-counter medications, was a nonsmoker, and had no known allergies. He also reported a remote history of substance and hallucinogenic abuse, although he had been abstinent for several years. He had never been hospitalized, had been adherent to and stable on clozapine for 7 years, and was highly functional in the community. On presentation, the patient was hypertensive and tachycardic but afebrile. His initial workup, including complete blood count with differential, was within normal limits; his valproic acid level was 45 mcg/mL. A clozapine level was not obtained upon admission; the most recent recorded level of 281 ng/mL (obtained 1 month prior) was substantially decreased from 553 ng/mL (obtained 1 year prior), which had been obtained when the patient was stable on clozapine (300 mg/day).

Several months prior to his presentation, he was diagnosed with a latent tuberculosis infection by a positive purified protein derivative skin test and negative chest X-ray. He started 16 weeks of anti-latent tuberculosis infection treatment with rifampin (600 mg/day), prescribed by the local health department. He preferred rifampin because of its shorter treatment duration, compared with isoniazid. But per outpatient notes, he was occasionally noncompliant with rifampin because he felt more “clear minded” when skipping doses. He was 70% adherent according to his rifampin refill history. Two weeks following initiation of rifampin, the patient’s paranoia worsened, and his outpatient provider increased his clozapine dose from 300 mg/day to 325 mg/day.

His clozapine dose was further increased to 350 mg/day 10 days later. The patient suffered a needle stick 17 days later and completed an HIV postexposure prophylaxis regimen with raltegravir (400 mg twice daily) and emtricitabine/tenofovir (200 mg/300 mg daily), with no additional changes to clozapine dosing.

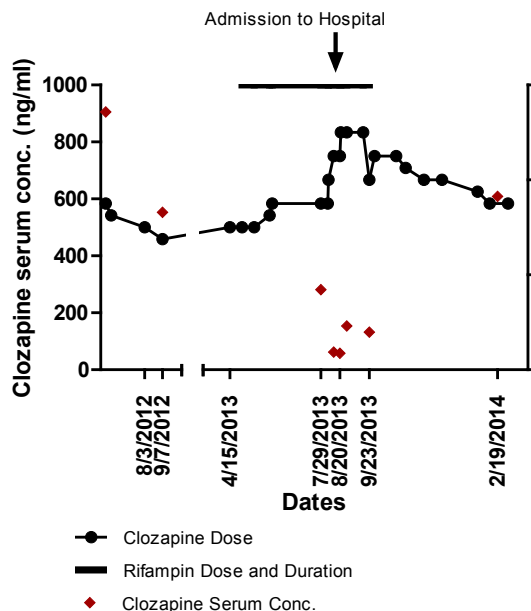
During admission, his clozapine dose was titrated from 350 mg to 500 mg daily over 14 days to target his presenting paranoia and delusions. His divalproex sodium dose was increased to 2,000 mg daily (on hospital day 8) to target persistently racing thoughts. His sertraline dose remained constant. His serum clozapine level increased from a low of 58 ng/mL (on hospital day 13) to 154 ng/mL (on hospital day 21), at which time the patient was discharged, with improvement in symptoms, although not back to baseline levels.

Mr. A completed rifampin treatment, and his clozapine dose was reduced from 500 mg/day to 400 mg/day, since his symptoms were well controlled. However, within 1 week, he suffered an increase in mania and paranoia, necessitating increases in divalproex sodium (from 2,000 mg/day to 2,500 mg/day) and clozapine (to 450 mg/day) doses. After symptoms were again controlled, divalproex sodium was reduced back to 2,000 mg/day, and clozapine was gradually tapered to 350 mg/day over several months. Presently, the patient has resumed working in the community. Changes in his clozapine daily dose and serum concentration levels relative to rifampin therapy and hospital admission are presented in Figure 1.

Discussion

The present case demonstrates the detrimental clinical impact of the drug-drug interaction between clozapine and ri-

FIGURE 1. Clozapine Dose and Serum Levels Relative to Rifampin Treatment and Hospital Admission



fampin. Using data from this case, in combination with data from two previous case reports, we propose steps that providers can take to minimize the effect of rifampin on the clinical stability of patients.

Our patient suffered a significant (89%) drop in clozapine serum concentration upon rifampin initiation, similar to the 83% decrease observed in the case reported by Joos et al. (6). The initial drop in our patient's clozapine serum level, from 281 ng/mL to 58 ng/mL, following admission to the hospital was likely a function of his improved compliance with rifampin during hospitalization, as opposed to before admission. His clozapine level had increased to 154 ng/mL at discharge, in response to an increased clozapine daily dose (500 mg/day up from 350 mg/day). However, during hospitalization, this level was still less than that recorded prior to rifampin treatment (553 ng/mL), at which point the patient was stable on clozapine 300 mg daily. The literature demonstrates a positive linear correlation between clozapine dose and serum concentration, but there are many factors that impact clozapine serum concentration, including adherence, concurrent medications, timing of

drug levels, genetic factors, gender, age, and nicotine/caffeine use (1–5, 8, 9). There is no evidence to suggest that our patient's recent postexposure prophylaxis regimen or change in divalproex sodium dose would have affected clozapine levels. His sertraline dose remained constant; he did not consume caffeine; and his clozapine serum levels were drawn at consistent times (3, 9). No information regarding his CYP450 or P-glycoprotein genotypes were available. Specific CYP450 or P-glycoprotein polymorphisms could result in chronically elevated (e.g., CYP2C19 *2/*2 poor metabolizers) or chronically low/normal (e.g., CYP2C19 non-*2/*2 extensive metabolizers) clozapine levels. These could contribute to the patient's observed low clozapine levels in the face of rifampin treatment if the patient had an extensive metabolizer phenotype or was a smoker, which is known to induce CYP1A2, leading to a 1.5-fold decrease in clozapine levels (2). However, the patient's previous, appropriate clozapine levels on typical clozapine doses, as well as his lack of a smoking history, argues against this phenomenon. Additionally, assessment of a single serum drug level during concomitant therapy with a potent enzyme inducer can be misleading, owing to notable variability in pharmaco-

kinetic parameters in this time context (10). Thus, the patient's variable rifampin adherence was the one known significant, confounding variable and likely the key offender leading to his subtherapeutic clozapine levels and decompensation.

Our patient had been taking rifampin for 3 months before hospitalization. He was likely able to avoid earlier hospitalization because of his excellent support system, suboptimal adherence with rifampin, limited increase in clozapine dose as an outpatient, and reasonable (although subtherapeutic) clozapine level prior to admission. His symptoms were unlikely the result of clozapine withdrawal psychosis because there was no evidence suggesting clozapine nonadherence.

Regarding the dosing adjustments made, our patient required a 67% clozapine dose increase to be stabilized sufficiently for discharge. Joos et al. (6) reported a 50% increase in dose during concomitant rifampin treatment, and Peritogiannis et al. (7) reported an 83% clozapine dose increase 2 weeks after rifampin was initiated in a patient to stabilize symptoms. These data suggest that a 50% dose increase should be targeted after rifampin initiation.

Management of clozapine therapy after discontinuing rifampin is equally challenging and requires close monitoring of symptoms and dose-related serious adverse effects, such as lowered seizure threshold and hypotension (8). In the present case, the patient's clozapine dose was reduced by 20% when rifampin therapy was complete. However, the patient required a subsequent increase in clozapine dose within 1 week to control re-emerging paranoia. The patient's re-emerging psychosis was likely a function of persistent induction of CYP450 enzymes by rifampin, since this drug's effect can persist approximately 2 weeks after medication discontinuation (4). Thus, any decrease in clozapine dose must be attempted very judiciously to minimize the risk of decompensation.

Conclusions

This case report described the interaction between rifampin and clozapine and

summarized the clinical implications of this interaction, with preliminary recommendations, demonstrating secondary prevention in psychiatry—reducing morbidity in an established case. We also demonstrated that knowledge of drug-drug interactions is important in preventing iatrogenic worsening of psychiatric conditions.

In summary, frequent (e.g., weekly) follow-up clinic visits after initiation and discontinuation of rifampin is imperative to attempt preventing clinical decompensation and potential adverse effects. These recommendations are made with the understanding that all dose changes should be ultimately based on the patient's current degree of symptom control and any evidence of adverse effects.

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The authors thank Dr. Kenan Penaskovic for his advice, encouragement, and assistance in the writing of this article.

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