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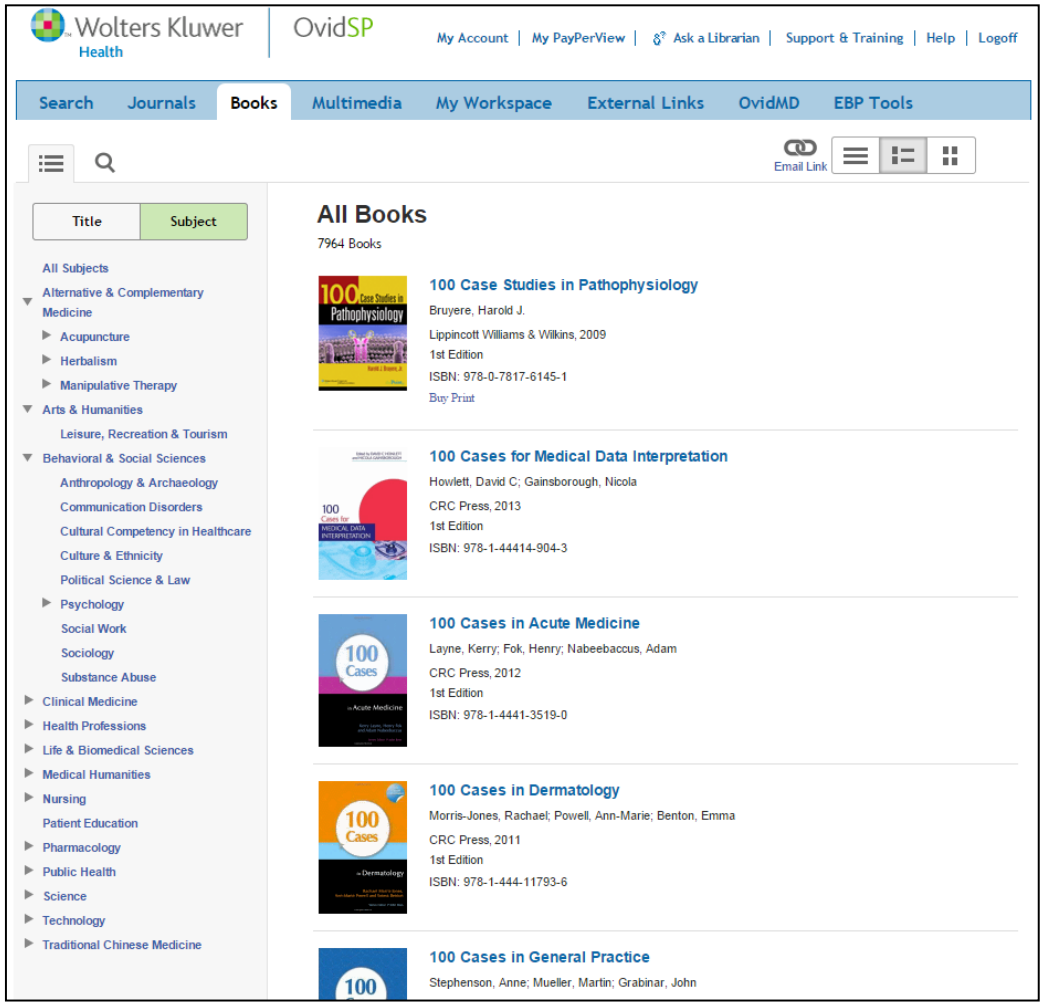
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aspects of cognition, temperament, and personality are attributable to genetic factors. Because these are the very domains that are affected in mentally ill patients, it would not be surprising to discover a similar level of genetic impact on mental illness, especially if we were able to assess this impact at a more discrete level, such as with endophenotypes.

### Individual Genes Have Modest Effects in the Development of Mental Disorders

Several types of data and observations suggest that any single gene is likely to have only a modest effect in the development of a mental disorder, and that when a mental disorder is present in an individual, it represents the effects of multiple genes, speculatively on the order of five to ten genes. This hypothesis also is supported by our failure so far to find single genes with major effects in mental illnesses. Some researchers, however, still consider it a possibility that genes with major effects will be identified.

### "Nature" and "Nurture" Interact Constantly within the CNS

In 1977, George Engel, at the University of Rochester, published a paper that articulated the biopsychosocial model of disease, which stressed an integrated approach to human behavior and disease. The biological system refers to the anatomical, structural, and molecular substrates of disease; the psychological system refers to the effects of psychodynamic factors; and the social system examines cultural, environmental, and familial influences. Engel postulated that each system affects and is affected by the others.

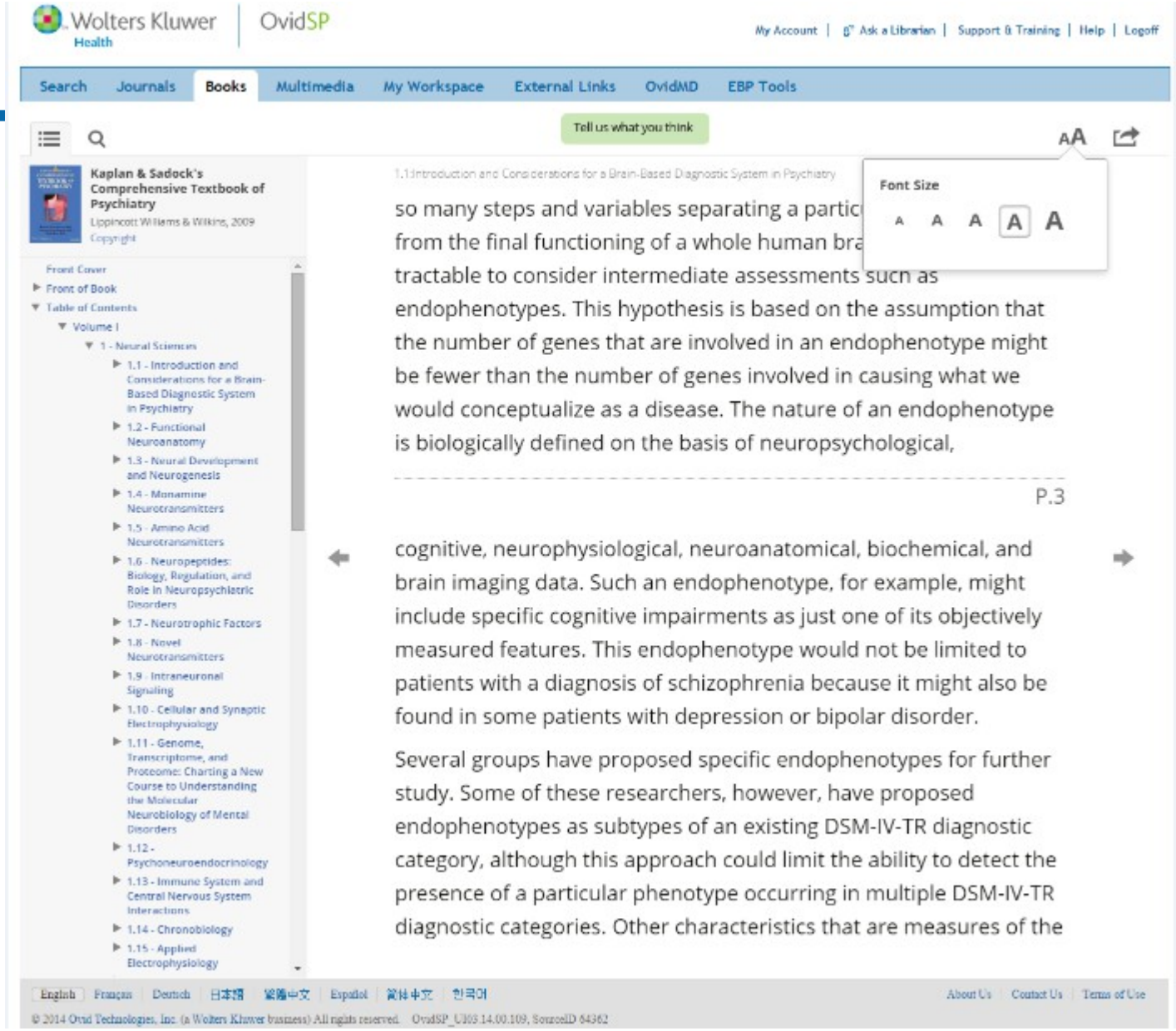
The observation that a significant percentage of identical twins are discordant for schizophrenia is one example of the type of data that support the understanding that there are many significant interactions between the genome and the environment (i.e., the biological basis of the biopsychosocial concept). Studies in animals have also demonstrated that many factors, including activity, stress, drug exposure, and environmental toxins, can regulate the expression of genes and the development and functioning of the brain.

### Mental Disorders Reflect Abnormalities in Neuroanatomical Circuits and Synaptic Regulation

Although genes lead to the production of proteins, the actual functioning of the brain needs to be understood at the level of regulation of complex pathways of neurotransmission and intraneuronal signaling, and of networks of neurons within and between brain regions. In other words, the downstream effects of abnormal genes are modifications in discrete attributes such as axonal projections, synaptic integrity, and specific steps in intraneuronal molecular signaling.

### Why Not a Genetic-Based Diagnostic System?

Some researchers have proposed moving psychiatry toward a completely genetic-based diagnostic system. This proposal, however, seems premature based on the complexity of the genetic factors presumably involved in psychiatric disorders, the absence of sufficient data to make these genetic connections currently, and the importance of epigenetic and environmental influences on the final behavioral outcomes resulting from an individual's genetic information.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1.1 Introduction and Considerations for a Brain-Based Diagnostic System in Psychiatry
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from the final functioning of a whole human bra
tractable to consider intermediate assessments such as endophenotypes. This hypothesis is based on the assumption that the number of genes that are involved in an endophenotype might be fewer than the number of genes involved in causing what we would conceptualize as a disease. The nature of an endophenotype is biologically defined on the basis of neuropsychological,
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cognitive, neurophysiological, neuroanatomical, biochemical, and brain imaging data. Such an endophenotype, for example, might include specific cognitive impairments as just one of its objectively measured features. This endophenotype would not be limited to patients with a diagnosis of schizophrenia because it might also be found in some patients with depression or bipolar disorder.
Several groups have proposed specific endophenotypes for further study. Some of these researchers, however, have proposed endophenotypes as subtypes of an existing DSM-IV-TR diagnostic category, although this approach could limit the ability to detect the presence of a particular phenotype occurring in multiple DSM-IV-TR diagnostic categories. Other characteristics that are measures of the
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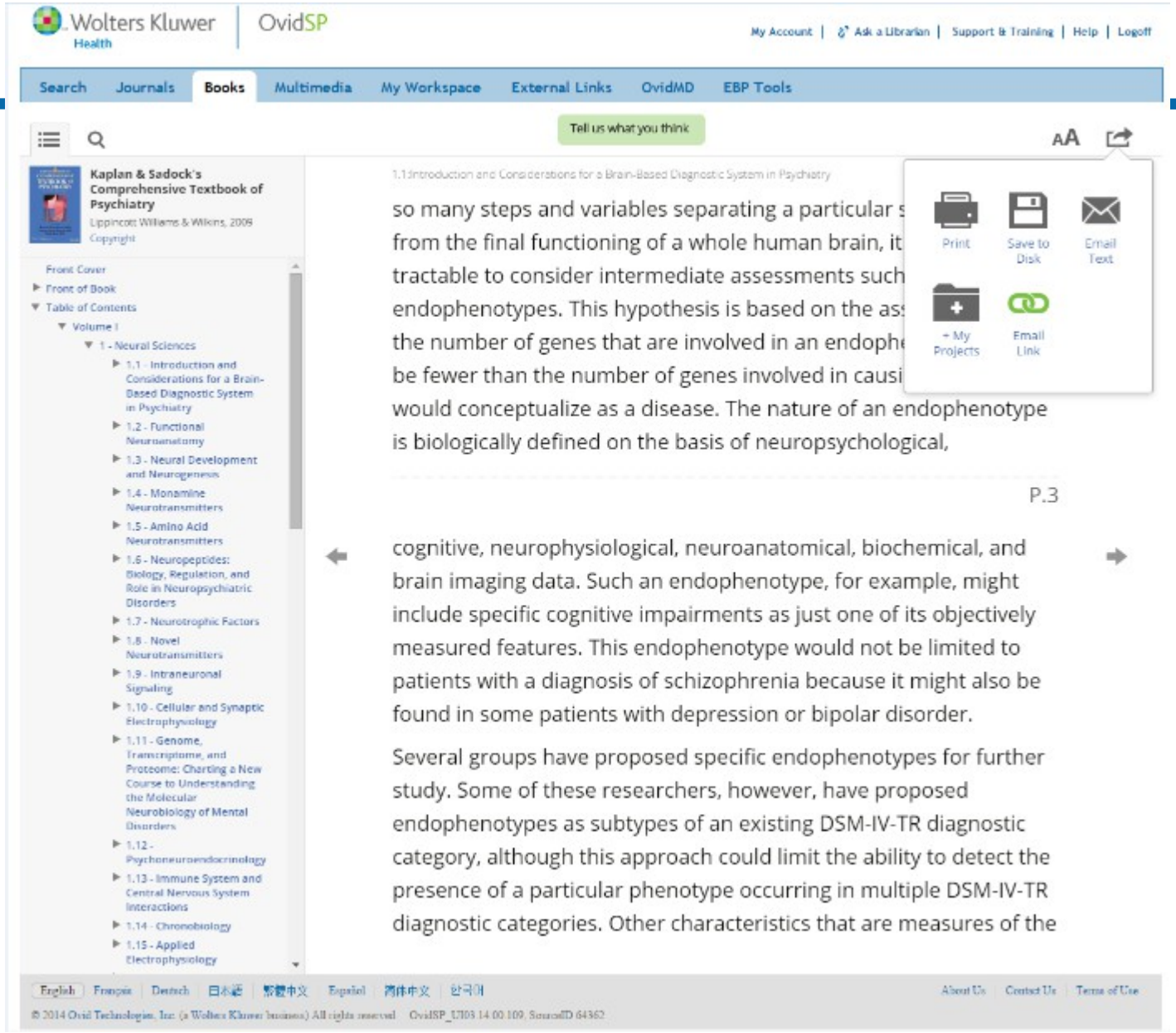
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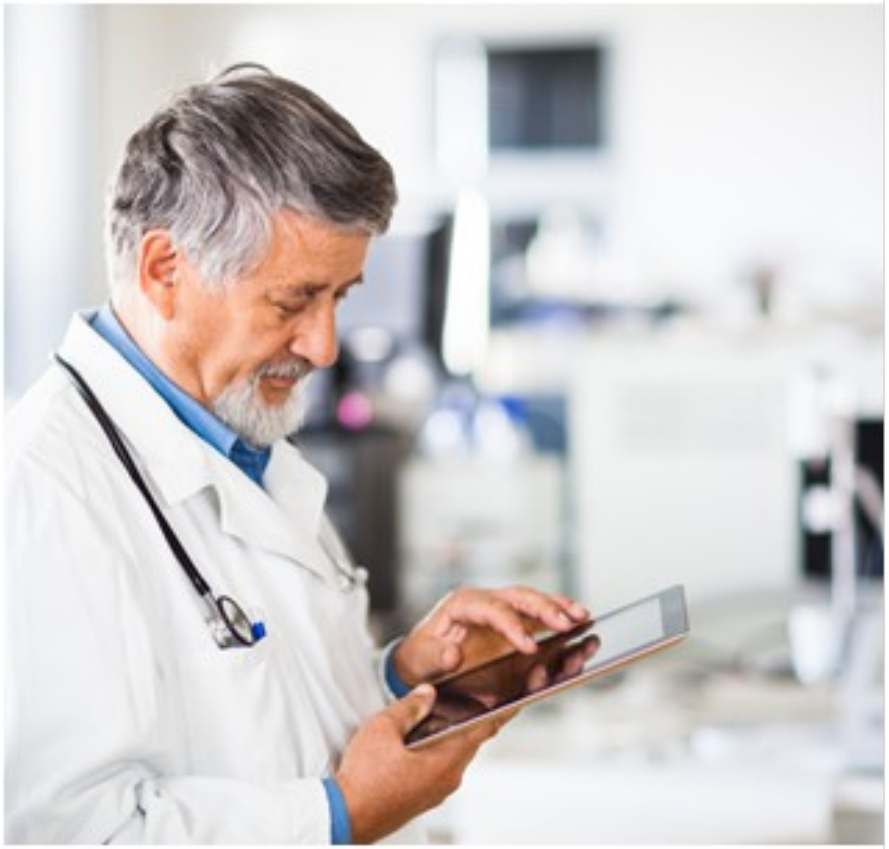

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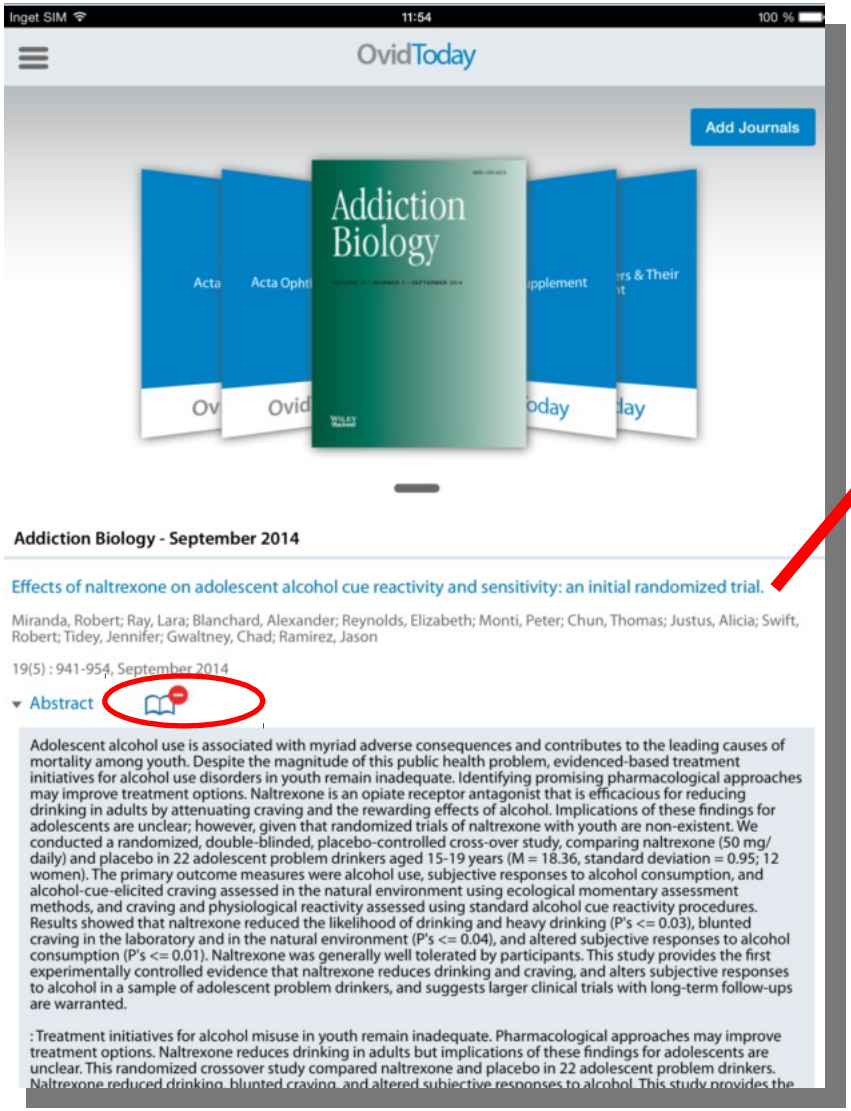
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Effects of naltrexone on adolescent alcohol cue reactivity and sensitivity: an initial randomized trial.
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19(5) : 941-954, September 2014
Abstract
Adolescent alcohol use is associated with myriad adverse consequences and contributes to the leading causes of mortality among youth. Despite the magnitude of this public health problem, evidenced-based treatment initiatives for alcohol use disorders in youth remain inadequate. Identifying promising pharmacological approaches may improve treatment options. Naltrexone is an opiate receptor antagonist that is efficacious for reducing drinking in adults by attenuating craving and the rewarding effects of alcohol. Implications of these findings for adolescents are unclear; however, given that randomized trials of naltrexone with youth are non-existent. We conducted a randomized, double-blinded, placebo-controlled cross-over study, comparing naltrexone (50 mg/daily) and placebo in 22 adolescent problem drinkers aged 15-19 years (M = 18.36, standard deviation = 0.95; 12 women). The primary outcome measures were alcohol use, subjective responses to alcohol consumption, and alcohol-cue-elicited craving assessed in the natural environment using ecological momentary assessment methods, and craving and physiological reactivity assessed using standard alcohol cue reactivity procedures. Results showed that naltrexone reduced the likelihood of drinking and heavy drinking (P's <= 0.03), blunted craving in the laboratory and in the natural environment (P's <= 0.04), and altered subjective responses to alcohol consumption (P's <= 0.01). Naltrexone was generally well tolerated by participants. This study provides the first experimentally controlled evidence that naltrexone reduces drinking and craving, and alters subjective responses to alcohol in a sample of adolescent problem drinkers, and suggests larger clinical trials with long-term follow-ups are warranted.
: Treatment initiatives for alcohol misuse in youth remain inadequate. Pharmacological approaches may improve treatment options. Naltrexone reduces drinking in adults but implications of these findings for adolescents are unclear. This randomized crossover study compared naltrexone and placebo in 22 adolescent problem drinkers.


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Effects of naltrexone on adolescent alcohol cue reactivity and sensitivity: an initial randomized trial
Robert Miranda, Lara Ray, Alexander Blanchard, Elizabeth K. Reynolds, Peter M. Monti, Thomas Chun, Alicia Justus, Robert M. Swift, Jennifer Tidey, Chad J. Gwaltney & Jason Ramirez
Brown University, Providence, RI, USA
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Keywords Adolescents, alcohol sensitivity, craving, cue reactivity, naltrexone.
Correspondence to: Robert Miranda, Center for Alcohol and Addiction Studies, Brown University, Box G-S121-5, Providence, RI 02912, USA. E-mail: Robert_Miranda_Jr@brown.edu
INTRODUCTION
Adolescence is a key period in the development of alcohol use disorders, with nearly 15% of youth meeting diagnostic criteria for alcohol abuse or dependence by 18 years of age (Merikangas & McClair 2012; Swendsen et al. 2012). Yet, less than one-third of treated youth experience sustained benefit from existing psychosocial interventions (Chung & Maisto 2006). Inadequate treatment for this age group is an important public health concern given that alcohol misuse during adolescence predicts future alcohol dependence in adulthood (Buu et al. 2011). Although pharmacotherapy research has expanded treatment options for adults with drinking problems, medication development for adolescents has not progressed. Randomized controlled pharmacotherapy trials for alcohol problems in the youth are few, and published reports bear substantial limitations that preclude inferences about the efficacy of the medication studied. This gap in knowledge impedes treatment practices, as the safety and efficacy of medications for adolescents cannot be inferred from adult data (Bridge et al. 2007).
Naltrexone is an opiate receptor antagonist that is efficacious for treating alcohol dependence in adults. In most clinical trials, naltrexone lowered the risk of relapse and reduced the frequency of drinking and heavy drinking days, with a modest effect size (g = 0.20; see Maisel et al. 2013). Considering its promise, researchers have attempted to elucidate the behavioral mechanisms by which naltrexone exerts beneficial effects. Retrospective patient reports in the initial clinical trials suggested that

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