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Review

A systematic review of psychostimulant treatment of negative symptoms of schizophrenia: Challenges and therapeutic opportunities

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ABSTRACT

Background: Primary negative symptoms of schizophrenia (NSS) contribute heavily to functional disability and treatment of these symptoms continues to be a major unmet need even when the positive (psychotic) symptoms are controlled. The modified dopamine (DA) hypothesis posits that positive symptoms are associated with increased DA activity in the mesolimbic tract whereas NSS and cognitive symptoms are associated with decreased DA activity in the mesocortical (frontal) region. Several studies have reported improvement in NSS with DA agonist use, but with varying degrees of risk for triggering psychotic symptoms, especially in the absence of concurrent antipsychotic drug treatment. This article aims to examine older and newer evidence suggesting that psychostimulants may have a potential therapeutic role in the treatment of NSS together with a thorough review of the potential risks and benefits of psychostimulant administration in individuals with schizophrenia.
Methods: A systematic search of relevant literature using electronic databases, reference lists, and data presented at recent meetings was conducted.
Results: Improvement of NSS after psychostimulant administration is reviewed both in challenge and treatment paradigms with various agents such as methylphenidate, amphetamine, and modafinil or armodafinil. The literature points to evidence that, used adjunctively, DA agonists may improve NSS without worsening of positive symptoms in selected patients who are stable and treated with effective antipsychotic medications. Several areas of inadequate study and limitations are identified including small study samples, single-site trials, varying rigor of bias control, the dose and the duration of adjunctive psychostimulant administration, and the potential for development of tolerance.
Conclusion: Large, controlled clinical trials to further characterize effects of psychostimulants on NSS in carefully selected patients are warranted.

1. Introduction

Distinctions between positive and negative symptoms of schizophrenia (NSS) have been recognized for more than 100 years, ever since Bleuler first coined the term *schizophrenia* in 1908 (Hanson et al., 2010). NSS include flattened/blunted affect, alogia, asociality, avolition/amotivation, anergia, and anhedonia (Rector et al., 2005; Stahl and Buckley, 2007). Such symptoms are intrinsic to the pathology of schizophrenia and associated with poor global psychosocial functioning, greater impairments in relationships, recreational and work activities, and reduced quality of life and social functioning (Milev et al., 2005; Stahl and Buckley, 2007).

Although positive symptoms of schizophrenia are often adequately managed by antipsychotic medications, at least one-third of patients demonstrate persistent negative symptoms, which have not responded to currently available antipsychotic treatment (Foussias and Remington, 2010; Hanson et al., 2010). In light of their association with impaired social and functional outcomes and the lack of available therapies for their management, clinicians and

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regulatory agencies have recognized the unmet need for effective strategies to treat NSS (Kirkpatrick et al., 2006; Laughren and Levin, 2006; Laughren and Levin, 2011). Hence, there is a clear need for the exploration of alternative pharmacological treatment mechanisms, beyond the traditional dopaminergic (e.g., D_2 receptor) and serotonergic (e.g., $5HT_{2a}$ receptor) blocking agents. This article aims to review older and newer evidence suggesting that psychostimulants may have a potential therapeutic role in the treatment of NSS together with a thorough review of the potential risks and benefits of psychostimulant administration in individuals with schizophrenia with the aim of refocusing clinicians' attention on factors that may influence how those effects are manifested. A review of the relevant literature revealed that a comprehensive compilation of published information on the effects of stimulants in schizophrenia has not been undertaken for more than 25 years. Thus, to address a perceived need to update more recent findings, we undertook a systematic review of relevant published literature on the effects of psychostimulant administration and factors mediating these effects.

The review includes a brief overview of the neurobiological hypotheses underlying the pathogenesis of NSS, a discussion of nontherapeutic and single-dose amphetamine challenge studies in subjects with schizophrenia, and in neuroimaging studies aimed at understanding the behavioral, clinical, and neurobiological effects of psychostimulants in subjects with schizophrenia. Later sections in this review examine both early and more recent studies of the therapeutic effects of psychostimulants on symptoms, function, and cognition, as well as nontherapeutic use of licit and illicit psychostimulant substances. It will articulate the rationale for use of psychostimulants in carefully selected schizophrenia populations and review the emerging evidence that psychostimulant compounds can improve negative symptoms of schizophrenia.

2. Literature review

2.1. Methods

A search of MEDLINE (1984-November 2011) and PsychINFO (1984-November 2011), was performed to find relevant articles. The search was limited to articles published after 1984 because several excellent articles by Lieberman et al. (1987a) and Chiarello and Cole (1987) have comprehensively reviewed earlier data. Where appropriate to illustrate particular points, details from selected studies covered in these prior reviews are included in the present review. An Ovid search of both databases was conducted using the search terms: (schizophrenia OR psychosis) AND (stimulant OR amphetamine OR methylphenidate). Results were limited to English-language articles reporting human studies, and included single case reports or small case series. The electronic search was supplemented by examining the reference lists of retrieved articles, and, where available, relevant abstracts and posters from scientific congresses.

2.2. Results

The initial literature searches yielded 1102 unique references. In addition to studies with the classic psychostimulants (i.e., amphetamine [AMP] and methylphenidate [MPH]), studies examining the effects of the wakefulness-promoting agents modafinil and armodafinil were also retained. Studies of other agents with dopaminergic/noradrenergic activity but not considered to be stimulants (e.g., mazindol and atomoxetine) were excluded from the present review. After the authors assessed the abstracts, 75 were deemed relevant to the present paper based on the following criteria: sufficient information on participants' background and clinical status, full information on dose, duration and type of drug treatment, and treatment outcome measures. The published manuscripts were included in the review and the reference lists of these manuscripts were reviewed for additional reports.

3. Neurobiological rationale supporting the use of psychostimulants for the treatment of NSS

3.1. Dopamine (DA) dysregulation hypothesis of schizophrenia

The DA hypothesis of schizophrenia proposes that DA dysregulation may be responsible for the positive, negative, and cognitive symptoms of schizophrenia (Howes and Kapur, 2009). DA receptor subtypes are differentially distributed within the brain. D_1 receptors are located throughout the neocortex (including the prefrontal cortex [PFC]) as well as nigrostriatal, mesolimbic, and mesocortical areas, whereas D_2 receptors are most densely expressed in the striatum, nucleus accumbens, and olfactory tubercle. D_3 receptors have a somewhat more circumscribed distribution with prominent expression in limbic areas (e.g., nucleus accumbens, olfactory tubercle), the ventral striatum, substantia nigra pars compacta, ventral tegmental area, hippocampus, and some cortical expression (Guillin et al., 2007; Beaulieu and Gainetdinov, 2011).

Based on antidopaminergic activity of antipsychotics and the psychotogenic effects of DA-enhancing drugs such as AMPs, positive symptoms of schizophrenia were empirically linked to the hyperactivity of DA transmission via D_2 receptors in subcortical regions such as the striatum and the nucleus accumbens (Laruelle et al., 2005; Toda and Abi-Dargham, 2007). In support of this hypothesis, numerous positron emission tomography (PET) and single-photon emission tomography (SPECT) imaging studies have demonstrated increased in vivo striatal DA functioning at D_2/D_3 receptors in patients with unmedicated schizophrenia (Laruelle et al., 2005; Howes and Kapur, 2009; Thompson et al., 2009). However, D_2-receptor antagonism does not appear to improve negative symptoms and cognitive dysfunction in schizophrenia, which led to a re-evaluation of the original DA hypothesis. Deficits in DA transmission at D_1 receptors, particularly in the mesocortical DA pathway and PFC, were subsequently proposed to contribute to negative symptoms and cognitive impairments (Guillin et al., 2007; Toda and Abi-Dargham, 2007). Even though supported by several lines of indirect evidence, direct evidence for the role of hypodopaminergic activity in the pathogenesis of NSS remains limited (Toda and Abi-Dargham, 2007).

The prevailing current view is that schizophrenia is characterized by deficits of DA in the PFC and excess DA in the striatum (Abi-Dargham, 2004; Guillin et al., 2007; Toda and Abi-Dargham, 2007); this opposing relationship of DA in the striatum and PFC may be mediated by the PFC-ventral tegmental and hippocampal-ventral tegmental loops (Goto and Grace, 2007). In addition, DA dysregulation may be specifically linked to psychosis and may be partially independent from other features of schizophrenia (Howes and Kapur, 2009). The relationship between D_1 dysregulation and cognitive functioning is likely best represented by an inverted U-shaped relationship, with optimal performance at stimulation levels that are neither too high nor too low (Goldman-Rakic et al., 2004). Alterations in the tonic and phasic release of DA may also play a role (Goto et al., 2007). In summary, while it is established that DA dysfunction is observed in schizophrenia, conclusive evidence supporting its causal role in the disorder is still lacking (Moncrieff, 2009). Given the proposed role of DA in the pathogenesis of cognitive impairments and negative symptoms in schizophrenia, DA agonists that either directly or indirectly activate D_1 receptors have been hypothesized to improve these symptoms (Tamminga, 2006; Gray and Roth, 2007; Mu et al., 2007; Toda and Abi-Dargham, 2007).

3.2. Other neurotransmitter hypotheses of schizophrenia

Abnormalities in other neurotransmitter signaling pathways are also implicated in the pathogenesis of schizophrenia. *N*-methyl-D-aspartate (NMDA) receptor hypoactivity may contribute to this because exposure to phencyclidine, a noncompetitive NMDA antagonist, results in a clinical