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Targeting hypothalamic-pituitary-adrenal axis hormones and sex steroids for improving cognition in major mood disorders and schizophrenia: a systematic review and narrative synthesis

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ABSTRACT

Cognitive deficits are a core feature of serious mental illnesses such as schizophrenia, major depressive disorder (MDD) and bipolar disorder (BD) and are a common cause of functional disability. There is limited efficacy of pharmacological interventions for improving the cognitive deficits in these disorders. As pro-cognitive pharmacological treatments are lacking, hormones or drugs that target the endocrine system may become potential candidates for 'repurposing' trials aiming to improve cognition. We aimed to study whether treatment with drugs targeting the hypothalamic-pituitary-adrenal (HPA) axis and sex steroids can improve cognition in patients with schizophrenia, MDD or BD. A systematic search was performed using PubMed (Medline), PsychInfo and clinicaltrials.gov, and a narrative synthesis was included. The systematic review identified 12 studies dealing with HPA-related drugs (mifepristone [n = 3], cortisol synthesis inhibitors [ketoconazole, n = 2], dehydroepiandrosterone [n = 5], fludrocortisone [n = 2]) and 14 studies dealing with sex steroids (oestradiol [n = 2], selective oestrogen receptor modulators [raloxifene, n = 7], pregnenolone [n = 5]). Positive trials were found for BD (mifepristone), MDD (dehydroepiandrosterone and fludrocortisone) and schizophrenia (dehydroepiandrosterone, raloxifene and pregnenolone). A replication of positive findings by at least two clinical trials was found for mifepristone in BD and raloxifene and pregnenolone in schizophrenia. The use of drugs targeting hormones related to the HPA axis and sex steroids is a promising field of research that might help to improve the cognitive outcome of patients with schizophrenia, bipolar disorder and major depressive disorder in the near future.

1. Introduction

Serious mental illnesses (SMIs) including schizophrenia, bipolar disorder (BD) and unipolar major depressive disorder (MDD) represent a serious health problem in terms of prevalence, suffering and disability (Vigo et al., 2016). Functional disability has also been associated with the presence of cognitive deficits (e.g., attention, memory and executive dysfunction), which are a common feature of SMI (Iosifescu, 2012). For many decades, cognitive deficits have been considered a core feature of schizophrenia and have been associated with mood symptoms in patients with acute episodes of BD and MDD. However, more recent knowledge suggests that cognitive deficits are also present in euthymic BD patients (Bora et al., 2010) and in patients with remitted MDD (Trivedi and Greer, 2014). Neuropsychological data do not provide evidence for differences in the affected cognitive domains in schizophrenia and major mood disorders (BD and MDD), although a subgroup of individuals with schizophrenia with more severe negative symptoms may be cognitively more severely impaired than those with MDD or BD

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(Bora et al., 2009).

The efficacy of the pharmacological interventions for improving cognitive processing in patients with schizophrenia or major mood disorders is limited. The evidence supporting the use of cognitive training interventions that can result in significant, albeit modest, improvements in specific cognitive functions (e.g., memory, attention, and problem solving) is greater than that supporting the use of pharmacological interventions (Keshavan et al., 2014; Revell et al., 2015; Wykes et al., 2011). In patients with schizophrenia, only a few studies have shown a benefit of pharmacological treatments (e.g., modafinil, amphetamine), and there is a lack of successful replication of these data. Furthermore, no positive results have been confirmed with larger samples in phase III studies to date (Harvey and Sand, 2017). In MDD and BD, cognitive remediation is increasingly studied, although there is a paucity of high-quality trials examining either pharmacological or non-pharmacological modes of intervention (MacQueen and Memedovich, 2017). Some authors have suggested the need to test the potential use of a number of promising new therapies, pharmacological agents or complementary medicines, but data are only now emerging (Solé et al., 2015). As pro-cognitive pharmacological treatments are lacking, hormones or drugs that target the endocrine system may become potential candidates for 'repurposing' trials aiming to improve cognition.

We aimed to perform a systematic and narrative review focusing on different endocrine systems to determine what has been done and what might be done in the future based on the current knowledge on the topic. This information may help both clinicians and researchers interested in the use of cognitive enhancers or the design of future clinical trials for improving cognition in people with SMI. A PICO scheme of the review is described in Table 1. We decided to include three clinical diagnoses (schizophrenia, MDD and BD) because they are SMIs that share cognitive impairments in similar cognitive domains. Longitudinal studies including recent-onset MDD, BD and schizophrenia-spectrum disorders suggest that the course of neuropsychological functioning does not appear to be diagnosis specific (Lee et al., 2015). Moreover, mechanisms linking hormones and cognitive functioning have also been considered in non-psychiatric populations and in the general population (Hogervorst, 2013; Lupien et al., 2005). Therefore, we considered drugs targeting hormones to enhance cognitive abilities across distinct SMIs in a similar way that antipsychotic drugs are used to improve psychotic symptoms in different SMIs (schizophrenia, MDD and BD). Drugs targeting the hypothalamic-pituitary-adrenal (HPA) axis and sex steroids have been reviewed. Most cognitive enhancement clinical trials targeting hormones in patients with schizophrenia, BD and MDD have focused on these hormone systems. We have reviewed clinical trials that used placebo, alternative drugs or pre-post changes in cognitive abilities and the outcome variable of improvement in neurocognitive domains. Our review was not focused on social cognition. For this reason, the potential use of oxytocin in improving social cognition has not been addressed in our review.

2. Methods

2.1. Search strategy

A systematic computerized search was conducted focusing on trials evaluating cognitive enhancers in schizophrenia, bipolar disorder and major depression. PubMed and PsycINFO databases (until January 2018) were used according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher et al., 2009). Additionally, this systematic computerized search was completed by hand-checking studies through references of included studies and review articles on the field of cognition and adrenal hormones. Furthermore, randomized controlled trials were also searched through the website Clinical Trials (www.clinicaltrials.gov) to include non-published trials.

In the systematic review dealing with the HPA axis, the following search terms were used: (dehidroepiandrosterone OR DHEA OR ketoconazole OR fludrocortisone OR mifepristone OR glucocorticoid OR mineralocorticoid OR cortisol OR HPA OR hypothalamic-pituitary-adrenal) AND (cognitive OR memory OR neuropsychology OR cognition) AND (depression OR bipolar disorder OR schizophrenia OR psychosis) AND trial.

In the systematic review dealing with sex steroids, the following search terms were used: (estrogens OR estradiol OR sex hormones OR gonadal hormones OR progesterone OR pregnenolone OR testosterone OR raloxifene OR tamoxifen) AND (cognitive OR memory OR neuropsychology OR cognition) AND (depression OR bipolar disorder OR schizophrenia OR psychosis) AND trial.

2.2. Inclusion criteria

Studies were only included if they met the following hierarchical inclusion criteria: (a) contained trials including patients with a diagnosis of schizophrenia, bipolar disorder or major depressive disorder, (b) were published in peer-reviewed journals, (c) written in English, German or Spanish, (d) and assessed the efficacy of the previously mentioned hormones as cognitive enhancers. Exclusion criteria were as follows: (a) other study designs rather than trials, (b) studies focusing on the efficacy of the hormone compounds in other symptomatic domains rather than cognitive symptoms, (c) studies exploring the acute effects (only one administration) of drugs targeting hormones on cognitive functioning.

2.3. Data collection and extraction

The literature search, data collection and extraction were conducted independently by two authors (AGR and JL). Disagreements were solved by consensus. From the selected articles, we excluded those that did not meet our inclusion criteria or that met our exclusion criteria. The last search was conducted on January 2018.

3. Results

3.1. HPA Axis

A total of 335 studies were identified, 221 in PubMed, 71 in PsycINFO, and 43 through other sources (www.clinicaltrials.gov). After duplicates were removed from the search (n = 42), 293 abstracts were retrieved for further scrutiny (Fig. S1 from Supplementary Material). Finally, 12 articles met our inclusion criteria and were included in this systematic review (List S1 from Supplementary Material). Further

Table 1
PICO scheme of the systematic review.

Patient, Population or Problem	Intervention	Comparison	Outcome
What are the characteristics of the patients or population? What is the condition or disease of interest?	What interventions are we are considering?	What is the alternative to the intervention?	What are the relevant outcomes?
Serious mental illnesses, including 3 main diagnoses: Schizophrenia, Major depressive disorder, Bipolar disorder. Shared condition: cognitive impairment	Treatment with drugs targeting hormone systems related to the hypothalamic-pituitary-adrenal axis or sex steroids	Placebo or any other intervention	Improvement in cognitive abilities