Neuropharmacology 72 (2013) 179–186

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Assessment of subjective cognitive and emotional effects of antipsychotic drugs. Effect by defect?

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ARTICLE INFO

Article history:
Received 16 November 2012
Received in revised form
11 March 2013
Accepted 23 April 2013

Keywords:
Antipsychotics
Psychosis
Compliance
Cognition
Emotion

ABSTRACT

Antipsychotic medication represents the first-line treatment for schizophrenia. While it is undisputed that antipsychotics ameliorate positive symptoms, the exact cognitive and emotional pathways through which the effect is exerted has remained unclear. The present study investigated the subjective effects of antipsychotics across various domains of cognition and emotion in both patients with psychotic symptoms and patients with other psychiatric diagnoses.

A total of 69 patients with a probable history of psychosis or psychotic symptoms and 26 patients with psychiatric diagnoses other than psychosis participated in a survey conducted over the Internet. Multiple control measures aimed to secure response validity. All patients were currently or had previously been treated with antipsychotic agents. A questionnaire comprising 49 items and measuring possible effects of antipsychotics on cognition and emotion was administered.

For 30 out of 49 items a clear response pattern emerged, which was similar for patients with psychotic disorders and patients with other diagnoses. Factor analysis of these items revealed three main effects of antipsychotic medication related to doubt and self-doubt, cognitive and emotional numbing, and social withdrawal.

Antipsychotic treatment appears to be connected to a number of negative subjective effects on cognition and emotion. Further studies are warranted to assess how these effects impact on the patients' subjective well-being and quality of life, as well as their association with antipsychotic efficacy on one hand, and adherence rates on the other. Induction of doubt and dampening of emotion may be one reason why antipsychotics work and at the same time offer an explanation why they are experienced as rather unpleasant and are eventually discontinued by many patients.

1. Introduction

In the 1950s the discovery of antidopaminergic medication led to a paradigm shift in the treatment of schizophrenia. Its introduction replaced less effective, often hazardous and invasive methods such as insulin shock (Doroshow, 2007) or leucotomy (Feldman and Goodrich, 2001). Until today, antipsychotic medication remains the unrivalled treatment of choice for schizophrenia. While the efficacy of dopamine antagonists on positive symptoms is well-documented a recent meta-analysis indicates that antipsychotic medication reduces symptoms merely at a moderate effect size (Leucht et al., 2009). Moreover, they are associated with adverse side effects. While most of the first-generation agents are associated with extrapyramidal symptoms, the newer second-generation antipsychotics have been found to induce somatic (especially metabolic) side effects, which are regarded as equally troubling by many patients (Schimmelmann et al., 2005). Not surprisingly, non-compliance constitutes a major obstacle in treatment (Dolder et al., 2002; Voruganti et al., 2008), occurring in 50–75% of the schizophrenia patients (Byerly et al., 2007; Kahn et al., 2008; Lieberman et al., 2005).

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http://dx.doi.org/10.1016/j.neuropharm.2013.04.039

1.1. How do antipsychotics work and affect cognition?

Our understanding about the biological pathways through which antipsychotic medication exerts its effect has expanded over the years but is still fragmented. Antipsychotics ameliorate positive symptoms (i.e., hallucinations and delusions) via both mesolimbic and mesocortical dopamine pathways (e.g., Sadock and Sadock, 2003; Stahl, 1999). Although these drugs also impact on other neurotransmitter systems, the antidopaminergic potential seems to represent the common denominator of all available first- and second-generation antipsychotic drugs (Kapur and Remington, 2001; Lambert and Naber, 2009; Sadock and Sadock, 2003). In contrast, assumptions relating to the cognitive and psychological mechanisms underlying antipsychotic effects have not yet fertiled to solid models. Elucidating these mechanisms may help to delineate pathogenetic models and the development of new therapeutic strategies for the treatment of positive symptoms.

The present study aimed to explore subjective cognitive and emotional effects of antipsychotic medication. Before we turn to the methodology of our investigation, research findings and theories on biological mechanisms of antipsychotic medication and their impact on cognition and affect will be summarized first.

A recent model about the interconnections between dopamine and psychotic symptoms (Kapur, 2003) postulates a triangular relationship among behavior, dopamine and schizophrenia symptomatology. Specifically, it is assumed that positive symptoms of schizophrenia are caused by a dysregulated dopaminergic activity that leads to excessive or random salience of stimuli: Certain stimuli "stick out" (i.e., receive overly weight), thereby fostering delusional ideation. According to Kapur, hypersalience is dampened by antipsychotics. In favor of this hypothesis are early observations suggesting that antipsychotics induce a state of "indifference" (Delay et al., 1952; Laborit and Huguenard, 1951), as well as studies reporting dysphoria (de Haan et al., 2004; Voruganti et al., 2001), often referred to as neuroleptic-induced negative syndrome (NIDS; Lader, 1993), and a certain emotional detachment under antipsychotic medication (Kapur et al., 2005; Mizrahi et al., 2006).

A plethora of studies have investigated the impact of antipsychotic medication on neuropsychological domains like executive functioning, memory and attention. These studies have produced somewhat conflicting findings (e.g., Mishara and Goldberg, 2004). Prior reports about beneficial effects of second-generation drugs on neurocognition (Keefe et al., 1999), have been increasingly called into question by recent reports asserting either no or merely weak effects on cognition (Keefe et al., 2007, 2004).

Another line of research that might provide insights into the psychological mechanisms of action of antipsychotic drugs is the examination of cognitive biases, such as jumping to conclusions (i.e., the tendency to make strong judgments on the basis of poor evidence, e.g. Garety et al., 1991), overconfidence in memory errors (Moritz et al., 2008, 2003), or a bias against disconfirmatory evidence (i.e., a strong tendency to stick to previously held opinions even in the face of substantial counter-evidence, Woodward et al., 2007, 2006, 2008). For example, in some of our studies we have collected tentative evidence that higher antipsychotic medication dosage is associated with decreased overall response confidence in memory tasks (Moritz et al., 2008, 2003). Conversely, the administration of L-Dopa seems to augment response confidence (Lou et al., 2011). Based on these preliminary findings, we have postulated that antipsychotic medication increases doubt and hesitance, which may extend to the psychopathological domain by attenuating delusional conviction (Moritz et al., 2008).

1.2. Methodological problems

Studies that have investigated how cognitive factors are modulated by antipsychotics are often hampered by several methodological difficulties. First, non-compliance and pretended compliance (i.e., the patients claim to be taking the medication when in fact they are not) is a problem in schizophrenia. Secondly, if psychotic symptoms attenuate over time and so do cognitive biases and deficits, this does not prove a causal relationship: observed effects might be due to other factors such as practice or the passage of time. Alternatively, cognitive biases and deficits may decrease over time parallel to a decline of symptoms other than productive psychotic phenomena (e.g., negative symptoms or impulsivity). Trials with patients on and off antipsychotics would be clearly desirable but are hard to conduct for obvious reasons (So et al., 2010), and very few antipsychotic-naïve patients or those who refuse intake are willing to undergo research. Correlational studies pose another problem, as it is hard to find a consensual way to express the effect of antipsychotic agents: equivalent dosages largely vary across different algorithms and are especially difficult to establish for second-generation antipsychotics (Taylor et al., 2009, p.11).

One way to shed light on the issue of how antipsychotics act on cognition and emotion is to directly enquire patients who are prescribed antipsychotic medication. The reliability of self-report measures in psychotic patients for the measurement of side effects has been demonstrated before (see Awad et al., 1995). For reasons pertaining to reliability, we recruited both a sample of patients with psychosis (schizophrenia or bipolar disorder with psychotic symptoms) and a non-psychosis group of patients prescribed antipsychotic agents in the context of augmentation strategies (Fountoulakis et al., 2004).

The questionnaire used for the present study included questions relevant to the theoretical models summarized in section 1.1. Following Kapur (2003) we included items on (dampened) perceptual and emotional processing, and also formulated items on doubt and subjective confidence, as our prior results (see above) suggest that confidence is modulated by antipsychotic medication as well (Moritz et al., 2008, 2003). We also considered items of the Subjective Well-Being under Neuroleptics scale (SWN; Naber et al., 2001). Further, questions relating to jumping to conclusions, cognitive inflexibility, attribution style, theory of mind, and emotion processing were posed. This was done because numerous studies suggest that these (partially overlapping) cognitive biases are involved in the formation and maintenance of schizophrenia positive symptoms and may thus be sensitive to the effects of antipsychotic agents. We were especially interested in cognitive flexibility,[5] as a review by So and coworkers (2010) tentatively suggests that antipsychotics may improve this function (however see also So et al., 2012).

Based on previous research by Kapur and coworkers (2003), we expected that patients would report a dampening of affect under antipsychotic medication. Furthermore, we expected that these drugs would also slow their thinking and decision-making (decreased jumping to conclusions), and would induce more doubt. The study was conducted over the Internet. We favored this strategy over a face-to-face interview, as the latter approach likely inflates socially desirable responses (Byerly et al., 2007; Klingberg et al., 2008). We aimed to recruit a mixed patient group including those

[5] Belief flexibility is a heterogeneous construct that can be examined in different ways, for example by self-report, neuropsychological tests like the trail-making test B or cognitive bias test like the so-called "bias against disconfirmatory evidence" paradigm (Woodward et al., 2007, 2008). Results from the latter domain suggest that incorrigibility is a state rather than a trait. In the present study it was defined as being able to question own opinions and attitudes.