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How antipsychotics work: The patients' perspective

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Abstract

Background: While much is known about the neuropharmacology and objective efficacy of antipsychotics, little is known about how these drugs act on psychosis from the patients' perspective. Most previous studies of the patient's perspective have focused on drug tolerability and acceptability—rather than their effects on psychosis per se.
Methods: The authors examined how antipsychotics work from a patient's perspective by analyzing their responses to a subjective questionnaire. Ninety-one patients with schizophrenia (cross-sectional component) and eight neuroleptic naïve patients (before and after treatment, longitudinal component) participated. The patients' responses to the questionnaire were analyzed using Principal Component Analysis (PCA) and general linear models.
Results: Analysis of the patients' responses showed that from their perspective the drugs were substantially more effective in: "help deal, help stop thinking, and make the symptoms not bother" rather than "take away" or "change my mind". This differentiation was clear in the raw data and was supported by a formal PCA. Two underlying factors – the first termed detachment and second eradication – explained 71% of the variance in the patients' perspective on how antipsychotics work for them. Neuroleptic naïve patients, who had no prior exposure, expected drugs to help with both detachment and eradication, but, changed their mind with just 6 weeks of experience with the medications.
Conclusions: From the patients' perspective the action of antipsychotics is best characterized by a detachment from symptoms—rather than an eradication or elimination of symptoms. They have more wide-ranging expectations prior to antipsychotic exposure, but, even 6 weeks of exposure is sufficient to change their mind in favor of detachment. This finding is consistent with some of the very earliest ideas that antipsychotics produced a state of "indifference" and is also consistent with the more recent, neurobiologically informed notions that antipsychotics work by dampening the salience of psychotic symptoms.

Keywords: Antipsychotics; Mechanism of action; Patient's perspective

1. Introduction

Since the serendipitous discovery of chlorpromazine almost half a century ago, advances in psychopharmacology, cognitive neuroscience and functional brain imaging techniques have allowed us to probe deeper into the objective actions of antipsychotic drugs. Studies at a neuropharmacological level have implicated a critical role for the dopamine system, though other receptors have also been implicated (Kapur and Mamo, 2003; Kapur and Seeman, 2001; Meltzer, 1999). Cognitive explanations have focussed on the action of the drugs on information processing or cognitive processes such as sensory motor gating (Geyer et al., 2001; Goldberg and Weinberger, 1996; Kumari and Sharma, 2002; Oranje et al., 2002; Stip, 1996). In addition, neuroimaging studies have drawn attention to the receptors where the drugs act and the regions where they change metabolism (Adolphs, 2003; Farde et al., 1988; Kapur et al., 2000; Nordstrom et al., 1993).

Abbreviations: ANT, attitudes towards medication treatment; DAI, Drugs Attitude Inventory; MARS, the Medication Adherence Rating Scale; M.I.N.I., Mini-International Neuropsychiatric Interview; PANSS, Positive and Negative Syndrome Scale; PCA, Principal Component Analysis; PETiT, Personal Evaluations of Transitions in Treatment; IQ, intelligence quotient; WAIS, Wechsler Adult Intelligence Scale.

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However, neither of these levels of analysis (neurochemical or elementary information processing deficits) are accessible to the patients. In fact, patients' perspective is very rarely, if ever, measured or discussed in routine research settings (Collins et al., 1991; Karow and Naber, 2002), although it has been suggested that general attitudes towards medication are key factors for adherence and recovery (Cabeza et al., 2000; Hogan and Awad, 1992; Hogan et al., 1983; Singh and Kay, 1979; Svedberg et al., 2003; Van Putten and May, 1978; Van Putten et al., 1981).

In the routine care of patients with schizophrenia the focus of treatment is on symptoms of psychosis—the delusions, hallucinations, disorganized speech and behaviour. While a considerable amount of scientific effort has been expended at this levels in describing how symptoms or clusters of symptoms change (Casey et al., 1960a,b; Ceskova and Svestka, 1993; Johnstone et al., 1978)—almost all of this work entails the clinicians' assessment of how the drugs are impacting the patient. While the patients are active collaborators in the treatment process (and the recipients of it), the patients' perspective on how antipsychotics work has received relatively little attention.

In the early 1950s, when psychological theories of schizophrenia were prominent and there was great interest in how drugs were experienced, a number of observations suggested that antipsychotics produced a state of "indifference" (Delay et al., 1952; Laborit and Huguenard, 1951) in patients. For example Elkes stated that "...patients continue to be subject to delusions and hallucinations, though they appear to be less disturbed by them" (Elkes j, 1954). These ideas were also captured by others and described as "distanciating agents" (Meurice, 1992) or "emotional restriction" (Belmaker and Wald, 1977). However, most of these descriptions were anecdotal in nature. More recent studies have focussed more on drug side-affects and their acceptability as well as studying the impact of drugs on the quality of life (Awad et al., 1995; Awad and Voruganti, 1999; Diamond, 1985; Hogan and Awad, 1992; Kampman et al., 2000; Thompson et al., 2000; Van Putten et al., 1981; Voruganti and Awad, 2002). For example, scales such as the Personal Evaluations of Transitions in Treatment (PETiT), the Attitudes towards medication treatment (ANT), the Drugs Attitude Inventory (DAI) or the Medication Adherence Rating Scale (MARS) focus on general attitudes towards psychotropic medication (Hogan et al., 1983; Kampman et al., 2000; Thompson et al., 2000; Van Putten et al., 1981; Voruganti and Awad, 2002). Thus, the earlier studies that focused on the patient's perspective were not systematic, whereas the more recent and controlled studies have focussed mainly on compliance/quality of life.

Thus, in the present study the authors have investigated the patients' perspective of how antipsychotics work for them in a large cross-sectional and a more selected longitudinal cohort in a systematic fashion. We first examined data from 91 chronically treated patients. The data showed us that the perspective of the patients could be captured by two main factors, and patients gave particular preference to the notion that antipsychotics created a state of "detachment" rather than "eradication" of symptoms. We then wanted to know if this expectation was innate (i.e. held even prior to experience with medications), or whether it arose after interaction with medications. To answer this we examined 8 neuroleptic naive subjects who were given the same questionnaire before ever trying antipsychotic treatment and after a 6-week trial of antipsychotic medications.

2. Method

2.1. Subjects

Patients were recruited from the inpatient and outpatient services of the Centre for Addiction and Mental Health, Toronto. REB approval and informed consent were obtained prior to these procedures. Patients were eligible to enter the study if they were aged 15–65 years, had an IQ>65, met the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-IV) (APA, 1994) for a psychotic disorder (schizophrenia, schizophreniform or schizoaffective), no significant medical or neurological illness, and no current substance abuse or dependence. Diagnostic inclusion criteria were ascertained by a trained psychiatrist using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Symptoms severity was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). IQ estimates were obtained with the digit symbol and information test from the WAIS (Sattler and Ryan, 1999).

2.2. Measures

Patients were interviewed for approximately 2 h by a trained psychiatrist who administered the PANSS to assess general psychopathology and to determine the principal psychotic symptom. For example, if the patient's main symptom was that secret police agents are bugging their phone, the questionnaire was then tailored to this principal belief. The main psychotic idea/ideas that were to be the focus of questioning were mutually agreed upon by the interviewer and the patient at the onset of the interview. This procedure was done to ensure that patients' responses would be related to their principal belief and not general attitudes towards medication. Patients were assessed with five statements in a 4-point anchored Likert format. The statements were chosen to reflect the words and concepts that have been reported in the past literature to reflect the patients' experience (Delay et al., 1952; Hogan et al., 1983; Kampman et al., 2000; Laborit and Huguenard, 1951; Thompson et al., 2000; Van Putten et al., 1981; Voruganti and Awad, 2002). Further, the exact choice of the wording of the statement was shaped by our clinical experience about the language that is commonly used by patients in the Canadian

Table 1
Results from principal components analysis

	Raw scores (SD)	PCA	
		Detachment	Eradication
Help me deal	2.06 (1.01)	0.72	0.2
Help me stop thinking	1.68 (1.09)	0.72	0.39
Not bother	1.83 (0.96)	0.88	0.03
Change my mind	1.17 (1.13)	0.14	0.86
Take away	1 (1.2)	0.20	0.82
Variance explained		51	20

Two main factors explained 71% of the variance; the first factor was termed "detachment" while the second factor was termed "eradication".

context. The statements were: (a) The medications help me deal with X, (b) The medication helps me stop thinking about X, (c) The medications make X not bother me as much, (d) medication have changed my mind of X and (e) medication have taken X away. When presented to patients the X was replaced with "neighbours" or "CIA" as per the patient's principal delusional/hallucinatory concern. Participants indicated the extent to which they agreed with each statement on a scale of 0, "not al all", to 3, "completely". It was reinforced that there was no correct or incorrect answers and confidentiality was guaranteed. Moreover it was emphasised that personal opinions were highly valued. In addition, to obtain further data regarding patient's perspective, at the end of the interview an open-ended question was asked: "What does the medication do for you, particularly in relation to X (we actually named their main symptom)?" Verbatim answers were recorded and main themes were extracted for descriptive purposes (Sandelowski, 1996, 2000).

2.3. Statistical analysis

A Principal Component Analysis (PCA varimax rotated) was performed with the five statements to elicit the underling variables that better characterize patients' answers. The Scree plot (visual break at the elbow) was used to inspect for factor solution accuracy. Factors 'score' means were obtained simply by summing the responses of the subsets of factored items and then dividing by the number of variables included in each factor. Repeated measure ANOVA and paired *t*-test were performed between the factor score means, both using the cross-sectional data to assess difference between the factors and between factor means before and after medication to asses change between visits. Open ended questions were used for descriptive purposes.

3. Results

The cross-sectional study group consisted of 91 subjects (female 16%), mean age of 33 (SD 12) years with a DSM diagnosis of schizophrenia (82%), schizoaffective disorder (15%), and schizophreniform disorder (3%). PANSS total mean score was 69 (SD 15) and PANSS positive score was 18 (SD 6). The mean IQ estimate was 96 (SD 13). All subjects were prescribed antipsychotic medication by their treating psychiatrist (74% atypical and 26% typicals). In the longitudinal study we included 8 subjects who were neuroleptic naïve at baseline and then we assessed them again after 6 weeks of a 6-week trial with antipsychotics. Diagnosis of this sub-sample of neuroleptic naïve patients were longitudinally confirmed as schizophrenia (62%), schizoaffective (25%) and schizophreniform (13%), mean age 27 (SD 12) and IQ estimate 95 (SD 14).

The five questions were inter-correlated and the resulting pattern of correlations suggested these items may represent two distinct types of patient belief about the effects of medication. To explore this possibility empirically, the correlation matrix was subjected to principal components analysis. Visual inspection of the Scree plot supported a two-factor solution (Cattell, 1966). These two factors explained 71% of the variance. The first factor included items such as "help me deal", "help me stop thinking" and "not bother" (we named this factor detachment). The second factor included the statements "change my mind" and "take away" and we have named this factor eradication. The factor component matrix is displayed in Table 1. There was a significant difference between the factors means ($t=7.82$, $p<0.001$; effect size (r)=0.451), the detachment factor had a mean of 1.86 (SD 0.8) while the eradication factor had a mean of 1 (SD 0.9). There were no correlations between gender, age, IQ and the "detachment" or "eradication" factors.

Furthermore, the authors wanted to know how experience with medications altered the patients' perspective: at

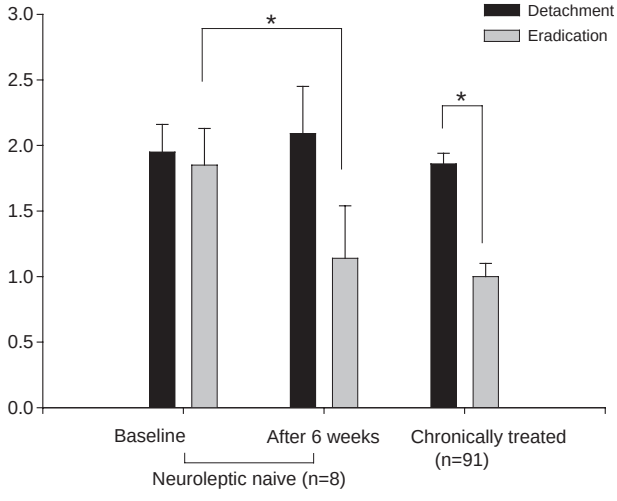

Fig. 1. There is a significant change in patients' perspective after having experienced their first trial with antipsychotics, in particular the eradication factor is reduced while detachment factors remains stable. Furthermore, this perspective of how antipsychotics work is consistent with the one reported by the chronically treated patients. Patients perspective of "how antipsychotics work" for them.

baseline, prior to experience with any medications, the neuroleptic naïve patients estimated that medications would impact on both detachment and on eradication (t: 0.76; $p=0.47$; effect size (r)=0.072). However, patients' responses changed after medication was started. While they significantly decreased their notion that medications will work via the eradication factor (baseline=1.85, after 6 weeks=1.14; $F=23$; $p=0.003$; effect size (r)=0.891) their expectations regarding the effects of medications on the detachment factor remained stable (mean baseline=1.95, after 6 weeks=2.09; $F=-0.19$; $p=0.676$; effect size (r)=0.177). Their final expectations, after 6 weeks of treatment, were not distinguishable from the more chronically treated patients (Fig. 1).

4. Discussion

The authors explored the patients' perspective on how antipsychotics work for their psychosis using a series of statements that reflect the words and concepts that have been reported in the literature. Analysis of the patients' responses showed that the drugs were substantially more effective in: "help deal, help stop thinking, and make the symptoms not bother" rather than "take away" or "change my mind". This differentiation was clear in the raw data and was supported by a formal PCA. It also seems that experience with medications is critical in arriving at this perspective because neuroleptic naïve patients, who had no prior exposure, expected drugs to help uniformly across the board; their expectations changed after just 6 weeks of experience with the medications.

4.1. Relationship with phenomenology

Our results, derived here with a standardised evaluation of patients and formal statistical evaluation, are consistent with earlier intuitive observations made by Laborit and Huguenard who reported in 1951 that patients given these drugs showed désintéressement in their surroundings. These observations were quite similar to those of Delay et al. who observed in 1952 an état d'indifférence (Delay et al., 1952; Laborit and Huguenard, 1951). Likewise, Elkes and Elkes stated "...patients continue to be subject to delusions and hallucinations, though they appear to be less disturbed by them" (Elkes j, 1954). In keeping with this historical stance we felt that the term "detachment" best captures the essence of the first factor—which contains the items "help me deal, help me stop thinking, and make the symptoms not bother". On the other hand, "take away and "change my mind" are statements that refer to the ability of the drug to remove the symptom from experience—and thus we have used the term "eradicate" to refer to this factor. We should also point out that the item "help me stop thinking" shares its loading on both Detachment and Eradication and this may have been related to its wording, since "stop" may have indeed connoted eradication of symptoms for some patients and hence biased their answers.

Chronically treated patients report that antipsychotics seem to "detach" them from their symptoms rather than "eradicate" them. This concept has also been captured by others, who have used terms such as "distanciating agents" (Meurice, 1992), and "emotional restriction"(Belmaker and Wald, 1977) to describe antipsychotics. In the same vein, Van Putten reported that patients with a "syntonic' response to antipsychotics say "I can cope with the voices better", "It brings me back into focus". These statements are also consistent with the responses that patients in this study gave to the open-ended questions which focused primarily on an improved ability to "think/focus", gain "control" and feel more "relaxed".

4.2. Relationship with the clinical picture

Most measurements of how antipsychotics act are reduced to a quantitative measure of symptoms' reduction, and this may have led to the assumption that antipsychotics reduce/eradicate symptom (Casey et al., 1960a,b; Ceskova and Svestka, 1993; Johnstone et al., 1978). However, it is widely known that for most patients antipsychotics provide only partial remission—and many aspects of psychosis as well as other aspects of the illness remain untouched. While some patients do actually achieve complete resolution of their delusions and hallucinations with antipsychotic treatment, for many patients a detachment from their symptoms is as good as resolution an antipsychotics can provide.

Patients' perspective of how antipsychotics work for them seem to be an observation drawn from experience: whereas before having had any experience with antipsychotic medication patients think that the medication will both "detach" and "eradicate" symptoms, after 6 weeks they seem to think that antipsychotics "detach" them from their symptoms rather than "eradicate" them. This final position of the first-episode recently treated patients is consistent with the perspective reported by the chronically treated patients that also report that antipsychotics "detach" them from their symptoms rather than eradicate them.

4.3. Relationship with neurobiological explanations

Taken together these descriptions fit well with recent neurobiological explanations of how antipsychotics work (Kapur, 2003). It has been proposed that antipsychotics are efficacious in psychosis because, by their biological actions (which involve dopamine at some level), they "dampen salience" of the subjective experience of delusions and hallucinations. In this scheme, derived mainly from neurobiological considerations about the role of dopamine, antipsychotic do not change thoughts or ideas primarily, but provide a neurochemical milieu

wherein new aberrantly salient associations and experiences are less likely to form and previously acquired aberrantly salient ideas and experiences are dampened (Clody and Carlton, 1980; Miller, 1987, 1989). Indeed, this is consistent with how patients experience their symptomatic improvement with antipsychotic treatment. Patients do not immediately abandon the psychotic idea, but report that the idea or percept "doesn't bother me as much" (Elkes j, 1954; Winkelman, 1954). Sigwald wrote "...the patient indicates that if the idea returns, he can easily put it out of his mind and forget it..." (Sigwald and Bouttier, 1953).

4.4. Limitations

This being the first systematic effort to study what antipsychotics do for the patients' psychotic symptoms from their perspective, there was little previous literature to build upon. Thus, there are several limitations which qualify our conclusions. First, we did not obtain measures of the general attitude of patient's towards medications (e.g. tolerability, acceptability, effects on quality of life) and nor did we obtain the more standard objective measures of side effects (AIMS, Simpson Angus). While our measures focus on a domain different from the above mentioned—nonetheless they are all related aspects of the drug-taking experience. Future studies aimed at understanding the relationship between the patients' perspective as well as the objective perspective will help clarify their relationship. Our longitudinal component of the study is in a small sample and has no control group to rule out the effects of mere repetition. While we acknowledge this limitation we would like to point out that despite the small sample the data are statistically very robust, and the fact that the neuroleptic naïve patients' change their views after drug exposure is a very plausible outcome.

5. Conclusion

The authors show that drugs not only quantitatively reduce symptoms, or partially eradicate them, they change the qualitative nature of the patient's experience of the symptoms. Our data suggest that the drugs work, from the patients' perspective, by creating a detachment from symptoms. In fact, this is how patients themselves characterize the effect of drugs, once they have had some experience with them. This phenomenological finding fits well with earlier descriptions and with more recent neurobiological explanations of how antipsychotics work (Kapur, 2004).

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