M. Barberá[1]
J. Sanjuán[2]
M. Munárriz[3]
E. Novella[2]
C. Santiago[3]
M. Simó[3]

Subjective experience with antipsychotics: quantitative evaluation

[1] Psychiatry Service
Hospital La Fe
Valencia (Spain)
[2] Hospital Clínico
Facultad de Medicina
Universidad de Valencia (Spain)
[3] Centro de Salud Mental de Burriana
Castellón (Spain)

Introduction. The subjective experience of psychotic patients with neuroleptics has been the purpose of many studies, considering its importance in treatment adherence, quality of life and outcome. Many authors have developed measurement instruments applicable in everyday clinical practice. The scale objectives defer in hues, but have the subjective perspective in common.

Method. Questionnaires designed for evaluating subjective experience with antipsychotics, appearing in PUBMED during the last 40 years, have been collected.

Results. Ten scales for evaluating the subjective experience with antipsychotics: NDS, DRI, DAI-30, DAI-10, ROMI, SWN, SWN (short version), MARS, ANT and PETiT, were found. Their advantages and limitations have been analyzed.

Conclusions. We have cheked out that the contents of each scale do not overlap. It is proposed to differentiate between «dysphoria response to neuroleptics» as an acute effect and the «subjective experience» as complex effect of long term compliance.

Key words:
Subjective experience. Side effects. Antipsychotis. Psychosis. Schizophrenia. Rating-Scales

Actas Esp Psiquiatr 2006;34(5):287-294

La experiencia subjetiva con antipsicóticos: evaluación cuantitativa

Introducción. La experiencia subjetiva de los pacientes psicóticos con el tratamiento neuroléptico, ha sido objeto de estudio ante su importancia en el cumplimiento, calidad de vida y pronóstico. Diversos autores han creado instrumentos de medida aplicables en la práctica clínica diaria. Los objetivos perseguidos por las escalas difieren en matices, pero tienen en común la perspectiva subjetiva.

Método. Se recogen los cuestionarios diseñados para la evaluación de la experiencia subjetiva con antipsicóticos, que han aparecido en Pubmed en los últimos 40 años.

Resultados. Se encuentran 10 escalas para la evaluación de la experiencia subjetiva con antipsicóticos: NDS, DRI, DAI-30, DAI-10, ROMI, SWN, SWN (versión corta), MARS, ANT y PETiT. Se analizan las ventajas y limitaciones de las mismas.

Conclusiones. Se comprueba que los contenidos que recogen cada una de las escalas no se superponen. Se propone diferenciar la «disforia a neurolépticos» como efecto agudo, de la «experiencia subjetiva» como efecto complejo del cumplimiento a largo plazo.

Palabras clave:
Experiencia subjetiva. Efectos secundarios. Antisicóticos. Psicosis. Esquizofrenia. Escalas de medición..

INTRODUCTION

The dominant trends of psychology and psychiatry, have focused on the measurement and quantification of normal or pathological mental phenomena for their study.

The subjective sensation the patient has when taking antipsychotic medication is not free from this rule. Thus, cognitive and emotional discomfort derived from compliance with neuroleptics have received several nomenclatures over the years, highlighting: «post-remission» (1967), «pharmacogenic depression» (1969), «akinetic depression» (1975-1978), «neuroleptic caused dysphoria» (1991), «neuroleptic depression» (1991), «neuroleptic induced anhedonia» (1991), «neuroleptic induced deficit syndrome» (1993)[1]. An attempt has been made to include the different clinical hues, with their repercussions, syndromically in order to measure them. The reason for this goes beyond the phenomenological interest on the evidence that when the subjective experience is unfavorable, prognosis clearly deteriorates.

Since the end of the 1970's, several authors have consecutively channeled their interest for this subject and crea-

Correspondence:
María A. Barberá Fons
Unidad de Psiquiatría de Adolescentes
Hospital La Fe
Av. Campanar, 21
46009 Valencia (Spain)
E-mail: mbarfons *a* yahoo.es

ted measurement instruments based on hypotheses having several profiles. There have been different and complementary approaches, focusing on different relevant aspects from the very early experiences. The underlying orientation is deduced from the scale names.

The first attempts are aimed at understanding «dysphoria», defined separately from the depressive syndrome of the patients undergoing psychotic recovery and the existing affective symptoms of the untreated patient. Singh et al. (1976)[2] indicate the impossibility of generalizing on questions of tolerance due to the heterogeneity of schizophrenia, inter-individual differences in pharmacological metabolism that may be fundamental in certain genetics, pharmacological profiles and interaction with the environment. They observe that dysphoria is not only related with extrapyramidal effects or pharmacokinetic specificities.

In 1985, Hogan et al.[3] explained a process of subjective experience consisting in successive steps: drug, plasma level, effect in cell receptor, organic repercussion, subjective interpretation of pharmacological effect and behavioral and psychological response of them subjected to specific individual conditions in time. The patient's interpretation on the pharmacological effect is that which they call «attitudes». They extend their view beyond dysphoria and intend to measure again.

Subsequent authors were concerned about questions on quality of life and compliance[1,4,5]. They perceived that the cognitive and emotional repercussions of the neuroleptics entail a good reason to reject the administration. In their scales, they understand that the responses to the questions formulated cannot be dichotomic, that they require a grading that reflects complexity.

Finally, they choose this quantitative method, thinking in favor of the pragmatic, in an attempt to extend this point of view to the daily clinical practice. With this intention, the design of some scales contemplates the short form[6,7] or aptitude to capture the subjective experience in different evolution moments.

ASSESSMENT SCALES OF SUBJECTIVE EXPERIENCE WITH ANTIPSYCHOTICS

We present a review of the scales published in the last 40 years. To do so, a revision has been made of journal articles appearing in PUBMED with the combination of the entries: subjective experience, dysphoria, neuroleptics, antipsychotic treatment, psychosis, schizophrenia and scale. Eight scales were obtained: NDS, DRI, DAI-30, ROMI, SWN, MARS, ANT and PETiT and there were two short versions of two of them: DAI-10 and SWN (short version). These will be reviewed in chronological order, stressing their characteristics, psychometric properties and limitations (table 1).

NDS (Van Putten and May, 1978)

The first to develop a scale to assess subjective sensations were Van Putten and May in 1978[8]. The NDS scale (Neuroleptic Dysphoria Scale) consisted in a semi-structured interview to assess the patient's response to four general questions: «How are you doing with the medication?, Does it affect your thinking?, Does it make you feel calm?, Do you think it is a good medication for you?» The rater should assess the patient's response and study it until translating it to a gradual score on the likert scale (from +11: maximum positive sensation; to –11: maximum negative sensation). This implies a response margin from +44 (maximum euphoric response) to –44 (maximum dysphoric response). They evaluated a total of 42 hospitalized schizophrenic patients who were administered 2.2 mg/kg of chlorpromazine, observing the consequences at the onset, at 4 and at 24 h. They repeated a dose of 2.2 mg/kg chlorpromazine at 25 h and another one of 4.4 mg/kg at 36 h, checking the consequences at 48 h. Twenty five patients (60 %) had a response that the authors considered «euphoric» and 16 (40 %) had a «dysphoric» response. Of the latter, the dysphoric response was so great in four of them, that the they refused to continue treatment and had to be excluded from the study. The authors did not find a relationship between the degree of dysphoria and psychopathology prior to the treatment or disease duration. It was also not possible for them to identify an association between the degree of dysphoria and treatment dose or plasma levels in later studies[9-11]. As main result of these studies, it was suggested that an initial dysphoric response was a potent predictor of the immediate result of the treatment and that the subjective effects associated to antipsychotic administration could predict long term compliance. Among the advantages of this scale, the possibility of a wide grading in the response and the use of acute disease phases stands out. Among the disadvantages, the requirement of interviewer training stands out in the first place. On the other hand, as this scale has few items and is perhaps excessively long, it does not allow for good discrimination of the complexity of the subjective phenomenon. The latter limitation is especially important in the follow-up of the out-patients. Thus, it is one of the best ways for subjective measurement of global response to neuroleptic treatment for acute phase psychotic patients.

DRI (Singh and Kay, 1979)

Almost contemporary to the previous authors, Singh and Kay coincide that early initiation of dysphoria in neuroleptic treatment predicts poor therapeutic result and unfavorable outcome[2]. In 1979, they published a retrospective study conducted in 58 patients diagnosed of schizophrenia who were sequentially administered placebo, neuroleptics (haloperidol or chlorpromazine) and anti-Parkinsonian agents[12]. During this period, they were given a semistructured interview of psychopathological assessment with six factors of the Brief Psychiatric Rating Scale (BPRS)

Table 1 Assessment scales of subjective experience with antipsychotics

	Author/year	No. of items	Study population/ application	Objective	Comments
NDS	Van Putten T and May PRA, 1978	4 items	Studied in 42 schizophrenic hospitalized patients Adequate for acute phase psychotic patients	Measurement of initial dysphoria to neuroleptic treatment	Semistructured interview Likert score (+11/–11) per item Total assessment: range of +44 to –44 (+44: maximum euphoric response; –44: maximum euphoric response)
DRI	Singh MM and Kay SR, 1979	6 specific items of BPRS to assess dysphoric state	Studied in 58 schizophrenic patients Adequate for acute phase psychotic patients	Measurement of dysphoria grade with neuroleptic treatment	Semistructured interview Score: dysphoric response index DRI > 12 = dysphoric DRI < 12 = not dysphoric
DAI-30	Hogan TP and Awad AG, 1983	30 (7 categories)	Studied in 150 chronic schizophrenic patients (54 % non-compliers) Applicable in different disease stages	Measurement of specific attitudes to perceived effects of the neuroleptics	Self-applied T/V score Bassed on patients opinions on their experiences with neuroleptics
DAI-10	Hogan TP and Awad AG, 1993	10	Applicable in different disease stages	Measurement of specific attitudes to perceived effects of the neuroleptics (short version)	Self-applied T/V score Simple, easily understandable and rapid to complete
PETiT	Voruganti LNP and Awad AG, 2002	30	Studied in 355 psychotic patients Usable in collaborating and cognitively conserved patients	Assessmento of: Subjective response and tolerability to NL Treatment compliance Impact of NL in quality of life	Self-applied structured questionnaire Rapid to complete
ROMI	Weiden PJ, et al., 1994	20 (2 sections)	Studied in 115 recently discharged schizophrenic out-patients Not valid in psychotic worsening periods	Assessment of subjective factors (attitude/behavior) influencing compliance	Semistructured interview Requires expert raters
SWN	Naber D, et al., 1995	38 (5 subscales)	Studied in 280 schizophrenic patients in remission To apply after acute disease phases	Investigation of «neuroleptic induced deficity syndrome» Measurement of subjective well-being and quality of life with neuroleptic treatment	Self-applied Items evaluated by 6 point likert scale Rapid application
SWN (short version)	Naber D, et al. 2001	20 (5 subscales)	Studied in 212 hospitalized schizophrenic patients (typical or atypical NL) Applicable in any disease stage	Develop a short version of SWN Application in studies on differences between neuroleptics	Self-applied Responses on 6 point likert scale Easy and rapid to complete
MARS	Thompson K, et al., 2000	10	Studied in 66 psychotic patients (out-patients + hospitalized ones) Valid in any therapeutic setting	Assessment of: Attitudes towards NL treatment Therapeutic compliance behaviors	Self-applied Yes/no response Cost/time effectiveness
ANT	Kampman O, et al., 2000	12 sentences (10 subsentences)	Studied in 106 hospitalized and out-patients complying with NL — 85 % psychotics Applicable in different disease stages	Assessment of: General attitude towards treatment Subjective experience Insight	Self-applied Grading 0-100 of each sentence: experience + positive to experience with + score

resulting as a reflection of dysphoric condition: depression, anxiety, cognitions of guilt and uselessness, suspiciousness/ ideation of persecutory type, hostility and suicidal ideation/behavior. Each factor was given a weight and the global sum was called dysphoric response index (DRI). Patients whose score was 12 (mean value of the DRI) or greater were considered «dysphorics», those who obtained a lower value were classified as «non-dysphorics». No relationship was

found between this response and the baseline value of dysphoria. Even more, it was observed that the patients classified as dysphorics began treatment with a lower degree of baseline malaise regarding the other group. No direct association between dysphoria and extrapyramidal reactions was observed, discarding anti-Parkinsonian treatment as effective relief of this subjective experience. This is where there is a difference regarding the Van Putten et al.[8,13] results. The latter involved akathisia and akinesia in the dysphoric response. The data reflected by these authors were exclusively applied to non-paranoid types of schizophrenia.

DAI-30 and 10 (Hogan et al., 1983)

Awad et al. are perhaps the authors who have most actively defended the concept of subjective response to neuroleptics[6,14,15]. Focusing on the scarce importance given to the discourse of the patient on treatment up to that moment, in 1983 they designed a self-applied scale called Drug Attitude Inventory (DAI) to measure subjective sensations of schizophrenic patients with the medication. The interest is found in knowing how the patient feels with it plus the knowledge or beliefs he/she has in this regards. This scale significantly correlates with Van Putten and May's NDS. It has 30 items (DAI-39)[14] and 10 items that are more specific of subjective experience in its reduced version (DAI-10)[6]. These are based on the true recorded and transcribed accounts of patients. Response options are only true/false. The items were selected by their capacity to discriminate the compliance grade in a statistically significant way. The subjects gathered could be divided, according to the factorial analysis, into seven categories: positive subjective experience, negative subjective experience, health models from the patient's perspective, experience of compliance control (it includes two factors), preventive effect of relapse and potential toxic effects derived from the treatment.

To validate it, it was administered to a population of 150 out-patients with the following criteria: understanding of the English language, diagnosis of schizophrenia and existence of a therapists who knew the compliance during the previous year (54 % were classified as non-compliers).

Among their conclusions, the authors pointed out that it was often not possible to distinguish if the patients responded in reference to the present subjective response or to the memory of previous experiences. Thus, «interoceptive conditioning» learning was stressed[16] as an important contributor to the subjective experience. Coinciding with their predecessors, they conceived that an initial dysphoric therapeutic response is a significant favoring factor of non-compliance[17-19], this experience being noticeably resistant to educational interventions.

Among the advantages offered by this scale, the fact that it is self-applied and thus not affected by the investigator's perspective is contemplated. As a disadvantage, it can be indicated that it does not allow the subject more than a dichotomic response, which we consider is especially biased when we try to capture something so dimensional as the subjective experience.

The DAI scale is probably that used most in the investigation of subjective response to antipsychotics, perhaps for its ease of application. Comparing it with other scales, the DAI has the advantage that it is more specific in relationship with the subject's attitudes towards antipsychotics. As has already been explained, data on compliance are inferred from it. All this makes it useful for controlled studies that aim to measure differences in subjective responses between treatments[20-23].

PETiT (Voruganti and Awad, 2002)

This same work group continues to go deeper into the study of neuroleptic induced dysphoria. Their approach includes the hypothesis of neuropsychopharmacological profile[24]. In 2002, they published another scale, The Personal Evaluation of Transitions in Treatment Scale (PETiT)[25]. It is self-applied, made up of 30 items based on comments from the patients in the firt person and, from a qualitative and quantitative point of view, it has good psychometric behavior, analyzed from the qualitative and quantitative point of view. The authors conceive the subjective experience with the neuroleptics as a link that connects antipsychotic treatment and aspects such as treatment adherence, quality of life and use of psychosocial resources. The objective of this scale is to control the changes perceived by the patients in the neuroleptic treatment longitudinally and approach the aspects influencing the clinical course (short, middle and long term). Among its advantages, its easy administration without requiring specific training stands out. It is proposed for out-patient monitorings. As a disadvantage, in principle, it is not adequate for patients in an acute disease phase nor for those who are not capable of observing clinical changes in their course.

ROMI (Weiden et al., 1994)

Based on their interest to study subjective experience with neuroleptic treatment, Weiden et al. focused their approach on the consequences on compliance[26]. In this way, they developed a semistructured in 1994 called Rating of Medication Influences (ROMI)[27]. This also correlated positively with the NDS and DAI scales. They had a sample of 115 recently discharged schizophrenic patients as study population. Originally, the scale was made up of 32 items, the initial 21 focused on compliance (items: 1-7) and non-compliance reasons (items: 8-21) from the patient's perspective and the final 11 (items: 22-32) aimed at the opinion of the rater in this regards. After obtaining kappa coefficients suggestive of limited interrater reliability, the third section of the scale was eliminated, it finally being made up of

20 items aimed at the reasons why the patients choose to comply (1-7) or reject the treatment (8-20). Among its advantages, it stands out that this scale covers more aspects than the previous ones, including, as we have already stated, those related to compliance. As disadvantages, it can be stated that it requires personnel training in dealing with out-patients affected by schizophrenia, and cannot be applied in acute phases or by untrained examiners. It would be appropriate for longitudinal studies of out-patients, where compliance was the key to investigate.

In this point, the authors suggest that each one of the scales would have a framework of different use. In this way, the Neuroleptic Dysphoria Scale (NDS) would be more indicated in acute phase psychotic patients, the DAI one would serve to measure specific subjective responses to drugs and the ROMI scale would be reserved for when it is considered there is the need to assess factors influencing compliance in out-patients[28-30].

SWN (Naber 1995 and Naber et al., 2001)

Naber et al. used the indisputable influence of the «Neuroleptic induced deficit syndrome»[31,34] on quality of life, to elaborate the Subjective Well-Being under Neuroleptic Treatment self applied scale (SWN)[1,7]. Their objective was to evaluate subjective well being with the medication, without going deeper into the distinction of the patient between treatment side effects and disease symptoms. This questionnaire has a strong relationship with the negative symptoms evaluated in the PANSS clinical scale and a modest relationship with the depression and quality of life scales. No statistically significant relationship has been found with questionnaires on extrapyramidal side effects. It originally had 54 items and was then reduced to 38. All are statements in the first person, 20 positive and 18 negative. The responses are recorded in likert format with six graded categories. This version, thus revised, was applied to a sample of 280 schizophrenic patients pending hospital discharge or those who had just been discharged. Application time was approximately 15-20 min. Five subfactors were analyzed in its statistical study: emotional regulation, self-control, mental functioning, social integration and physical functioning. This scale has shown good psychometric properties: internal consistency, test-retest reliability and sensitivity to change in a sample of 105 schizophrenic, schizoaffective or schizophreniform patients[35-37]. The authors suggest that the subjective experience with neuroleptic treatment is measurable and should be considered in the clinical practice and clinical trials of neuroleptic treatments, as it clearly interferes in quality of life and compliance. They also indicate the limited correlation existing between psychopathological improvements observed and subjective wellbeing. Among its advantages, this scale is contemplated as having easy and fast administration, it being possible to apply in principle in most of the disease stages. A clear disadvantage, in our opinion, is that the formulation of the items does not allow for good discrimination between subjective effects that can be attributed to treatment and the disease or other causes.

The short version of SWN was elaborated by an analysis of the SWN items, using the data of 212 hospitalized schizophrenic patients under treatment with typical or atypical antipsychotics. It is made up of 20 items, four for each subscale, maintaining sufficient internal consistency and good construct validity. It was used in a comparative study among atypical neuroleptics (olanzapine, risperidone and clozapine), the scores being favorable to the first one. After verifying the limited relationship between psychopathology and subjective wellbeing again, the authors concluded with the reflection that a satisfactory treatment should include reduction of psychotic symptoms and contribution to enjoyment of life with quality[7].

MARS (Thompson et al., 2000)

Thompson et al.[4] analyzed the deficiencies of the DAI scale to approach neuroleptic treatment compliance. Based on certain «attitudes» taken from the DAI scale items and on «problematic behaviors» contemplated in The Medication Adherence Questionnaire (MAQ)[38], they conducted a study with 66 psychotic patients to elaborate the Medication Adherence Rating Scale (MARS) questionnaire. It is made up of 10 yes/no answer questions that approach the complexity characterizing neuroleptic treatment compliance, including subjective experience. The authors state that compliance behavior is an all/nothing dichotomic, so that it is possible to differentiate between good and bad complying patients according to the scores reached in the scale. It is self-applied and has greater internal validity than the DAI scale according to its creators. Among the advantages it offers, are its easy and fast administration, and that its validety for any clinical context. Among its deficiencies, it is found that it does not contemplate the relationship existing compliance, among symptomatic severity and pharmacological side effects.

ANT (Kampman et al., 2000)

Practically simultaneous with the previously mentioned authors, Kampman et al. once again consider the compliance problems of neuroleptic treatment inherent to the patients affected by psychotic symptoms (insight, stigma and cognitive dysfunction among others). Starting from the limitations of the DAI (dichotomic sentences) to assess the variation of attitudes toward treatment as a reference, they created the Attitudes Towards Neuroleptic Treatment (ANT) scale using a study of 106 hospitalized patients and out-patients who complied with neuroleptic treatment, 85 % of them affected by a psychotic picture[5]. Their objective was to create a useful assessment method to survey attitudes towards treatment applicable before this could affect the subjective experience and during the follow-up

while under its effects. This scale is made up of twelve sentences divided, in turn, into ten sub-sentences evaluated from 0 to 100. Thus, the highest scores imply greater subjective experience in each one of the twelve sections. With it, a quantitative grading of general attitudes, subjective experience and insight is obtained. Among the advantages offered by this scale, the approach to the attitude of non-compliance and expectations of this behavior, that is frequently difficult to detect in the clinical practice, stands out. It is fast and easy to use, but must be correctly introduced to the patient.

DISCUSSION

Review of the measurement scales of experience with neuroleptic treatment, indicates different perspectives of quantitative approach of a same concept. In spite of their common intentionality, they differ in hues of content, extension, application framework and administration form. Most are relatively short in length[39].

The following stand out among the advantages they contribute: advice on the perception of treatment effect by the patient, utility as a screening method to detect high risk situations of non-compliance and indication in comparative studies.

Among the disadvantages, the difficulties inherent in the quantitative method to examine the treatment effects in psychotic patients and the absence of a clear criterion to define neuroleptic dysphoria and the subject experience as such are contemplated. Some of the scales presented have begun with the suggestion and consensus of experts, not the patients themselves, a fact that multiplies the global problem of measurement in psychopathology.

Except for the NDS, DRI and ROMI, all are self-applied, a fact which, in principle, tries to avoid the bias of the interviewer. The DAI, PETiT, ROMI, MARS and ANT scales consider the long term treatment consequences (attitudes, compliance, psychosocial functioning). The NDS is general in its approach and the others are multidimensional. In all of them, their specific application for psychotic patients who comply with neuroleptic treatment is contemplated. The NDS limits its use to acute disease phases while the ROMI and SWN are not adequate in these periods. The rest are, in principle, applicable to any stage.

Of the contents reviewed, the differentiation of two pictures within the subjective experience to antipsychotics can be stressed (table 2). The first one has a relationship with the immediate experience produced by the medication and would correspond with that which Van Putten called «neuroleptic dysphoria»[8,11]. It has been suggested that this acute unpleasant sensation may be related with the degree of D2 blockage on the limbic level. De Haan et al. (2003)[37] tried to establish the level of D2 occupation necessary to cause the optimum grade of subjective experience with both olanzapine and haloperidol by the SPECT. Using a test conducted in a group of 24 schizophrenic patients, they reached the conclusion that the ideal grade of occupation would be about 60 %-70 %. According to this model, dysphoria to neuroleptics would be closely related with the pharmacodynamic, molecular and pharmacogenetic profiles of each patient (polymorphisms in D2). This hypothesis coincides with that proposed by Kapur (2003)[40]. He suggested that the antipsychotic mechanism is found in the decrease of the exaggerated emotional effect derived from excessive dopamine release.

On the other extreme is the subjective experience as middle-long term complex experience. It deals with the ex-

Table 2 **Differences between acute effect «neuroleptic dysphoria» and middle-long term effect «subjective experience»**

	Narcoleptic dysphoria	Subjective experience
Time of appearance	Immediate effect with first doses	Elaboration with chronic use
Possible etiopathogenic explanation	Grade of D2 blockage	Sum of experiences with medication, personality and patient setting
Relationships	Genetic vulnerability Pharmacodynamics	Affectation of subjective quality of life
Clinical repercussion	Rejection Immediate intolerance	Poor long-term compliance
Most adequate scales	NDS DRI	DAI ROMI SWN MARS ANT

planations elaborated by the patient on the drug effect. This theory, generated consciously and unconsciously, is the result of the initial dysphoria associated to personality, insight grade, perception of drug efficacy, middle term side effects and family and cultural setting. It has a relationship with quality of life. It is a much more complex construct, in which many more variables have an influence, than in neuroleptic dysphoria. We believe that it is very important to differentiate between these two concepts and thus choose the most appropriate measurement for its study.

REFERENCES

1. Naber D. A self-rating to measure subjective effects of neuroleptic drugs, relationships to objective psychopathology, quality of life, compliance and other clinical variables. Int Clin Psychopharmacol 1995;10(Suppl. 3):133-8.
2. Singh MM. Dysphoric response to neuroleptic treatment in schizophrenia and its prognostic significance. Dis Nerv Syst 1976;37:191-6.
3. Hogan TP, Awad AG, Eastwood MR. Early subjective response and prediction of outcome to neuroleptic drug therapy in schizophrenia. Can J Psychiatry 1985;30:246-8.
4. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. Schizophr Res 2000;24:241-7.
5. Kampman O, Lehtinen K, Lassila V, Leinonen E, Poutanen O, Koivisto AM. Attitudes towards neuroleptic treatment: reliability and validity of the attitudes towards neuroleptic treatment (ANT) questionnaire. Schizophr Res 2000;45:223-34.
6. Awad AG. Subjective response to neuroleptics in schizophrenia. Schizophr Bull 1993;19:609-18.
7. Naber D, Moritz S, Lambert M, Pajonk FG, Holzbach R, Mass R, et al. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. Schizophr Res 2001;50:79-88.
8. Van Putten T, May PR. Subjective response as a predictor of outcome in pharmacotherapy: the consumer has a point. Arch Gen Psychiatry 1978;35:477-80.
9. Van Putten T, May PR, Jenden DJ, Cho AK, Yale C. Plasma and saliva levels of chlorpromazine and subjective response. Am J Psychiatry 1980;137:1241-2.
10. Van Putten T, May PR, Marder SR. Subjective responses to thiothixene and chlorpromazine. Psychopharmacol Bull 1980;16:36-8.
11. Van Putten T, May PR, Marder SR, Wittmann LA. Subjective response to antipsychotic drugs. Arch Gen Psychiatry 1981; 38:187-90.
12. Singh MM, Kay SR. Dysphoric Response to Neuroleptic Treatment in Schizophrenia: its relationship to Autonomic Arousal and Prognosis. Biol Psychiatry 1979;14:277-94.
13. Van Putten T. Why do schizophrenic patients refuse to take their drugs? Arch Gen Psychiatry 1974;31:67-72.
14. Hogan TP, Awad AG, Eastwood R. A self report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. Psychol Med 1983;13:177-83.
15. Hogan TP, Awad AG. Subjective response to neuroleptics and outcome in schizophrenia: a re-examination comparing two measures. Psychol Med 1992;22:347-52.
16. Barofsky I. Behavioral therapeutics and the management of therapeutics regimens. En: Sackett DL, Haynes RB, editores. Compliance with therapeutic regimens. Baltimore: John Hopkins University Press, 1976; p. 100-9.
17. Awad AG, Hogan TP. Subjective response to neuroleptics and the quality of life: implications for treatment outcome. Acta Psychiatr Scand 1994;380(Suppl.):27-32.
18. Awad AG, Hogan TP, Voruganti LN, Heslegrave RJ. Patients' subjective experiences on antipsychotic medications: implications for outcome and quality of life. Int Clin Psychopharmacol 1995; 10(Suppl. 3):123-32.
19. Awad AG, Voruganti LN, Heslegrave RJ, Hogan TP. Assessment of the patient's subjective experience in acute neuroleptic treatment: implications for compliance and outcome. Int Clin Psychopharmacol 1996;11(Suppl. 2):55-9.
20. Awad AG, Voruganti LNP, Heslegrave RJ. A conceptual model of quality of life in schizophrenia: description and preliminary clinical validation. Qual life Res 1997;6:21-6.
21. Voruganti L, Cortese L, Oyewumi L, Cernovsky Z, Zirul S, Awad A. Comparative evaluation of conventional and novel antipsychotic drugs with reference to their subjective tolerability, side-effect profile and impact on quality of life. Schizophr Res 2000;43:135-45.
22. Hofer A, Kemmler G, Eder U, Honeder M, Hummer M, Fleischhacker WW. Attitudes toward antipsychotics among outpatient clinic attendees with schizophrenia. J Clin Psychiatry 2002;63:49-53.
23. Voruganti L, Cortese L, Owyeumi L, Kotteda V, Cernovsky Z, Zirul S, et al. Switching from conventional to novel antipsychotic drugs: results of a prospective naturalistic study. Schizophr Res 2002;57:201-8.
24. Voruganti L, Slomka P, Zabel P, Costa G, So A, Mattar A, et al. Subjective effects of AMPT-induced dopamine depletion in schizophrenia: correlation between dysphoric responses and striatal D(2) binding ratios on SPECT imaging. Neuropsychopharmacology 2001;25:642-50.
25. Voruganti LN, Awad AG. Personal evaluation of transitions in treatment (PETiT): a scale to measure subjective aspects of antipsychotic drug therapy in schizophrenia. Schizophr Res 2002; 56:37-46.
26. Weiden PJ, Mann JJ, Dixon L, Haas G, DeChillo N, Frances AJ. Is neuroleptic dysphoria a healthy response? Compr Psychiatry 1989;30:546-52.
27. Weiden PJ, Rapkin B, Mott T, Zygmunt A, Goldman D, Horvitz-Lennon M, et al. Rating of medication influences (ROMI) scale in schizophrenia. Schizophr Bull 1994;20:297-310.
28. Weiden PJ, Rapkin B, Zygmunt A, Mott T, Goldman D, Frances A. Postdischarge medication compliance of inpatients converted from an oral to a depot neuroleptic regimen. Psychiatr Serv 1995; 46:1049-54.
29. Weiden PJ, Aquila R, Emanuel M, Zygmunt A. Long-term considerations after switching antipsychotics. J Clin Psychiatry 1998; 59(Suppl. 19):36-49.
30. Weiden PJ, Mott T, Curcio N. Recognition and management of neuroleptic noncompliance. En: Shirqui C, Nasrallah H, editores. Contemporary Issues in the treatment of schizophrenia. Washington: American Psychiatric Association Press, 1995; p. 411-34.
31. Liddle PF, Barnes TR. The subjective experience of deficits in schizophrenia. Comparative Psychiatry 1988;29:157-64.
32. Windgassen K. Treatment with neuroleptics: the patient's perspective. Acta Psychiatr Scand 1992;86:405-10.

33. Lader M. Neurolpeptic induced deficit syndrome: old problem, new challenge. J Psychopharmacol 1993;7:392-3.
34. Lewander T. Neuroleptics and the neuroleptic-induced deficit syndrome. Acta Psychiatr Scand Suppl 1994;380:8-13.
35. De Haan L, Lavalaye J, Linszen D, Dingemans PM, Booij J. Subjective experience and striatal dopamine D(2) receptor occupancy in patients with schizophrenia stabilized by olanzapine or risperidone. Am J Psychiatry 2000;157:1019-20.
36. De Haan L, Weisfelt M, Dingemans PM, Linszen DH, Wouters L. Psychometric properties of the Subjective Well-Being Under Neuroleptics scale and the Subjective Deficit Syndrome Scale. Psychopharmacology 2002;162:24-8.
37. De Haan L, Van Bruggen M, Lavalaye J, Booij J, Dingemans PM, Linszen D. Subjective experience and d(2) receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. Am J Psychiatry 2003;160:303-9.
38. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self reported measure of medication adherence. Med Care 1986;24:67-74.
39. Voruganti L, Awad AG. Neuroleptic dysphoria: towards a new synthesis. Psychopharmacology 2004;171:121-32.
40. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology and pharmacology in schizophrenia. Am J Psychiatry 2003;160:13-23.