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A brief version of the Subjects' Response to Antipsychotics questionnaire to evaluate treatment effects

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ABSTRACT

Background: Monitoring patients' experiences with antipsychotics may help to improve medication adherence and outcome. We aimed to develop a shorter version of a comprehensive 74-item self-report questionnaire suitable for routine monitoring of desired and undesired effects of antipsychotics.

Methods: Included were patients with psychotic disorders from seven mental health care organizations in The Netherlands, using antipsychotic medication, who completed the Subjects' Response to Antipsychotics (SRA-74). Exploratory factor analysis (EFA) and similarity analysis based on mutual information were used to identify the latent factor structure of the SRA. Items were reduced according to their metric properties and clinical relevance upon consensus by an expert panel, using a Delphi procedure of three rounds. We determined the internal consistency of the shorter version using Cronbach's alpha.

Results: SRA data of $N = 1478$ patients (mean age of 40 years, 31% females) were eligible for analysis. EFA extracted thirteen factors from the SRA-74, including four factors for desired effects (e.g. recovery of psychosis, cognition and social functioning) and nine factors for undesired effects (e.g. weight gain, flattened affect and increased sleep). Based on this solution 12 items were eliminated for statistical reasons. The expert panel eliminated another 28 items with redundant content, resulting in a 34-item version. The SRA-34 includes 10 desired and 24 clinically relevant undesired effects. Both the subscales for desired and undesired effects have a Cronbach's alpha coefficient of 0.82.

Conclusions: The SRA-34 can be used to evaluate desired and undesired effects of antipsychotics in routine clinical practice and research.

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1. Introduction

Schizophrenia is a chronic psychiatric disease, commonly necessitating lifelong treatment with antipsychotics. Antipsychotics increase the burden of disease, when they affect patients' physical, psychological, sexual and social functioning (Voruganti et al., 2002). The patients' experience of desired and undesired effects in response to antipsychotic medication has been identified as a strong predictor of adherence and outcome (Naber et al., 1994; Awad et al., 1996). Systematic monitoring of the balance between desired and undesired effects with

antipsychotics is important for disease management (Budd et al., 1996; Perkins, 2002). This requires a reliable and valid instrument.

Self-report is most optimal for the detection of often neglected, yet disturbing experiences, such as sexual side effects (Peuskens et al., 1998; Knegtering et al., 2003). Furthermore, self-report may save time and costs in routine clinical practice. Existing self-rating scales assessing experiences with antipsychotics either focus on quality of life, like the Subjective Well-being on Neuroleptics (SWN) (Naber, 1995; Naber et al., 2001) and the Personal Evaluation of Transitions in Treatment (PETIT) (Voruganti and Awad, 2002), or focus on undesired effects, like the Liverpool University Neuroleptic Side Effect Rating Scale (LUNERS) (Day et al., 1995), and the Glasgow Antipsychotic Side-effect Scale (GASS) (Waddell and Taylor, 2008), see Wolters et al. (2009). In contrast, the Subjects' Response to Antipsychotics (SRA) is a comprehensive assessment of 74 desired and undesired effects attributed to antipsychotic medication, divided over

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8 subscales (Wolters et al., 2006). It is constructed of lay term expressions, based on original patient statements which may be easier understood than some of the clinical terms in the LUNTERS (Waddell and Taylor, 2008). However, our own experience with the SRA-74 suggests that patients especially those with concentration difficulties find it a long questionnaire with many questions addressing the same clinical effect. Reducing the total number of items within the range of other scales (about 30 items) (Day et al., 1995; Naber et al., 2001; Voruganti and Awad, 2002; Waddell and Taylor, 2008) would increase its feasibility for screening purposes. The subscale structure of the SRA-74 has been established by a priori assumptions (Wolters et al., 2006) and so far, the latent structure has not been evaluated using more advanced statistical methods. The current study therefore explored the latent structure of the SRA by exploratory factor analysis (EFA) in a large cohort of patients with psychotic disorders. The main aim was to develop a shorter version of the SRA, while maintaining the latent structure.

2. Methods

2.1. Questionnaires

The SRA-74 consists of one subscale of 24 desired effects, seven subscales of 30 undesired effects of antipsychotics and 20 miscellaneous undesired effects not belonging to a subscale; Appendix A1 (Wolters et al., 2006). The subscales have good internal consistency (Cronbach's alpha 0.69–0.93) and test–retest reliability (Pearson's r correlation 0.39–0.60). The SRA is rated on a 3-point scale (not present/yes, mild/yes, severe). Patients received the SRA by mail to complete it at home. In case of difficulties in completing the questionnaire they received help from a trained nurse.

Trained nurses rated the level of psychotic symptoms using the Positive and Negative Symptom Scale for Remission (PANSS-R) (Opler et al., 2007). The patient's psychiatrist or case manager rated psychosocial functioning using the Global Assessment of Functioning scale (GAF; DSM-IV) (APA, 1994). A psychiatrist diagnosed each patient according to the Diagnostic and Statistical Manual of Mental Disorders—4th edition (DSM-IV) classification system (APA, 1994). Medication use over the past year was retrieved from medical records and confirmed with the patient.

2.2. Subjects

Patients with psychotic disorders receiving mental health care in the north of The Netherlands, Amsterdam and Dordrecht were invited to participate in the annual screening of their mental and physical health by the Pharmacotherapy Monitoring and Outcome Survey (PHAMOUS). Investigations were carried out between 2006 and 2010, in accordance with the latest version of the Declaration of Helsinki. Included were patients with psychotic disorders (DSM-IV codes 295.4–295.9, 297.1, 298.8 and 298.9), who used antipsychotics for at least one month and completed the SRA (maximally 2 items missing). In case a patient had participated in successive annual assessments, the first available measurement was selected for evaluation.

2.3. Latent structure

Exploratory factor analysis (EFA) was used to identify the latent factor structure of the SRA-74. Since one item of the SRA (about menstruation) was completed only by female participants, factor analysis was conducted on 73 items. In addition to EFA, we performed similarity analysis to visualize the latent structure of the SRA-74 (for a detailed description of the procedures, see Appendix A2).

2.4. Item reduction

Within each factor, items with loadings of $r < 0.30$ on all factors, cross-loading of $r > 0.30$ on two or more factors, or loading on a factor with a low main factor loading of $r < 0.50$ were considered non-factorable (Comrey and Lee, 1992). Non-factorable items were eliminated if there was no consensus about their clinical relevance by the expert panel (see below). Factorable items with high factor loadings ($r > 0.80$) and/or a highly similar content within the same factor were considered redundant. Of each pair of redundant statements, the item with least specific, most ambiguous or multi-interpretable (e.g. feelings that can be interpreted both literally and metaphorically) content was eliminated upon consensus by the expert panel.

2.5. Delphi procedure

A Delphi procedure consisting of three consecutive rounds was used to reach consensus about the clinical relevance of the items in the questionnaire (Hsu and Sandford, 2007). The expert panel, all native Dutch speaking, consisted of six psychiatrists, two neurobiologists and two psychologists. In the first round, the panelists received the full questionnaire including the results of the statistical analysis by e-mail. The experts were asked 1) to rank order the clinical relevance of the non-factorable items dropped for statistical reasons and 2) to mark redundant items until maximally three items within each factor were retained. Clinical relevance was defined as being relevant for a patient to (dis)continue antipsychotic therapy. In the second round, the panelists received a new proposal for the shortened questionnaire, including a summary of the arguments for item elimination or preservation. The experts were asked whether they agreed with the proposed item reduction. If not, they were asked to replace redundant items and to re-rank the clinical relevance of each item. In the third and final round, consensus was reached about the final version of the questionnaire. Items with consensus rates of more than 75% agreement within the panel were retained.

2.6. Statistics

Descriptive analyses and factor analysis were performed using Statistical Package for Social Sciences (PASW-18). Missing SRA-responses were imputed for patients with maximally 2 items missing, using the default settings of the multiple imputation method and random number generator (Mersenne Twister) of PASW-18. This cut-off was chosen as maximally 2.7% of responses were missing per patient which can be considered sporadically missing responses. Patients who completed all items of the SRA were compared to patients with maximally 2 items missing and to excluded patients (missing 3 or more items), with respect to: gender, age, duration of illness and inpatient/outpatient status using chi-square tests for categorical variables and Mann–Whitney U tests for continuous variables.

Prevalence rates of SRA items were based on dichotomized scores (no/yes). Factor analysis was conducted on the original 3-point scale of the SRA. The responses on the desired effects were reversed prior to factor analysis to obtain uniform scaling. The extraction method for EFA was Generalized Least Squares. The rotation method was Direct Oblimin with Kaiser Normalization, assuming a certain degree of correlation between factors (e.g. *increased sleep* with *sedation*). The number of factors to be retained was predefined by the Kaiser's criterion (eigenvalues ≥ 1). Kaiser–Meyer–Olkin (KMO) and Bartlett's tests for sphericity were calculated to test whether the relationships among variables in the sample are adequate for factor analysis.

The internal consistency of the final version of the SRA was calculated for the factorable items within the desired effects subscale and undesired effects subscale. A Cronbach's alpha ≥ 0.80 indicates good internal consistency (Streiner, 2003).

3. Results

3.1. Subjects

The number of patients included for evaluation was $n = 1478$ (66%) out of $n = 2241$ patients with psychotic disorders receiving routine outcome assessments in the selected mental health care organizations between 2006 and 2010. Excluded were $n = 142$ (6%) patients not using antipsychotics at the time of the interview, and $n = 621$ (28%) patients having three or more SRA-items missing. In the included sample, no systematic patterns were observed among missing SRA-items and no items had more than 5% missing values. Hence 325 (0.3%) missing values were imputed for those patients with maximally 2 missing SRA-items ($n = 272$). Included patients ($n = 1478$) had a mean age of 40.1 (SD 11.4) years and consisted of $n = 462$ (31.3%) females (Table 1). Patients missing maximally 2 items had similar characteristics as patients without missing items ($n = 1206$) except for a longer duration of illness (respectively 15.6 versus 13.5 years; $p < 0.05$). Excluded patients ($n = 621$) had a similar duration of illness than patients without missing items ($n = 1206$), but were on average 4 years older (43.9 versus 39.9 years; $p < 0.001$), consisted of relatively more female (38.6% versus 31.1%; $p < 0.001$) and admitted patients (36.7% versus 28.3%; $p < 0.001$).

On average, patients attributed 13 (56%) out of 24 desired effects to antipsychotics, compared to 18 (38%) out of 50 undesired effects. Patients most frequently reported the desired effects of the SRA-74, including 'My emotions have returned' (93%), 'My memory has improved' (92%) and 'I am more active' (90%); most frequently reported undesired effects were 'I need more sleep' (62%), 'My weight has increased' (60%) and 'I get physically tired more easily' (57%). All other statements had a prevalence rate above 5%.

3.2. Latent structure

Exploratory factor analysis extracted fourteen latent factors from the 73 SRA-items, explaining a total variance of 58% (Table 2). The correlation matrix of the data was considered factorable because the EFA solution passed the Kaiser-Meyer-Olkin (KMO) test with a value of >0.60 and the Bartlett's test of sphericity was significant

($p < 0.001$). All factors had high main factor loadings (0.58–1.00), except for factor 13 (0.31). Factor 13 consisted of items with heterogeneous content and low factor loadings.

Visual inspection of the similarity matrix gave comparable results as our exploratory factor analysis. All items with high factor loadings shared a relevant degree of mutual information (similarity). Within each factor, at least two items shared an amount of $I > 0.20$ mutual information, except for factor 13 (Appendix A3). The items within factor 13 displayed no sign of mutual dependence. Those items may have converged in an artificial factor because they had low prevalence rates in common. Thus only factors 1 to 12 and factor 14 were deemed reliable.

3.3. Item reduction

The number of items of the questionnaire was reduced to 52 after the first Delphi round of the expert panel and to 34 items after the second round. In total, 23 items were identified as non-factorable, see Fig. 1. Of those, 11 items were retained because of their clinical relevance. Of the 52 factorable items, 28 redundant items were eliminated upon consensus of the expert panel. For example, #33 'My feelings have returned' was considered ambiguous and #11 'My thoughts are calmer' could be substituted by the more specific statement #03 'I can think more clearly'. Similarly, the statements #16 'I think more slowly' and #50 'I move more slowly' were considered redundant to #13 'I react more slowly'. Some of the items were eliminated because they may be stigmatizing or evoke socially desired answers, e.g. #70 'My sex drive is too low'; or because the statement may be dependent on external factors such as the potentially limited social network of inpatients, e.g. #36 'I have more difficulty keeping up with conversations'. After the third Delphi round, consensus was obtained about the 34-item questionnaire (Appendix A4), consisting of 10 desired and 24 undesired experiences with antipsychotics.

3.4. Internal consistency of SRA-34

The internal consistency was acceptable for the desired subscale (Cronbach's $\alpha = 0.82$; 9 factorable items), as well as for undesired subscale ($\alpha = 0.82$; 14 factorable items) of the SRA-34.

4. Discussion

The SRA-34 is a unique questionnaire to measure a combination of relevant self-reported desired and undesired effects in response to antipsychotic medication. This is the short version of the SRA-74 questionnaire retaining the latent structure by covering 10 desired and 24 undesired effects of antipsychotics. The SRA-34 is internally consistent, having Cronbach's alpha values within the range of the previously reported values for the subscales of the SRA-74 (Wolters et al., 2006). Thus the SRA-34 can be considered a quick and reliable instrument to guide pharmaco-therapeutic treatment in clinical practice.

Exploratory factor analysis of the SRA-74 revealed new symptom dimensions, in addition to the original subscale structure as proposed by Wolters et al. (2006). First, desired effects were divided into four factors (recovery from psychosis, improvement in cognition, attention and social functioning). Second, we identified depressive symptoms as a factor, independent of other emotional experiences. The other factors remained the same (increased sleep, appetite and weight, slowed down behavior, sexual problems, EPS, social withdrawal and flattened affect). Similarity analysis was useful in identifying a number of items that did not belong to any of the factors, such as 'dry mouth' and 'increased salivation'. Of those, experts retained the most clinically relevant items in the SRA-34 according to the Delphi consensus method.

Table 1
Patient characteristics ($n = 1478$).

	Sample ($n = 1478$)	
	N or mean	% or SD
Gender (female)	462	31%
Age (years)	40.1	11.4
Duration of illness (years)	13.9	9.9
PANSS-positive	2.1	1.0
PANSS-negative	2.3	1.1
GAF symptoms	53.0	14.1
GAF functioning	52.5	13.2
Inpatients	415	28%
Antipsychotics		
Haloperidol	83	6%
Risperidone	202	14%
Olanzapine	268	18%
Clozapine	186	13%
Quetiapine	104	7%
Aripiprazole	78	5%
Other antipsychotic	254	17%
Combinations	303	21%
Number of co-medications	2.0	2.2
Reported desired effects (of 24 items)	13	56%
Reported undesired effects (of 50 items)	18	37%

Values were missing for the following variables: duration of illness ($n = 302$; 14%), PANSS ($n = 75$; 3%), GAF symptoms ($n = 365$; 17%) and GAF functioning ($n = 544$; 25%).

Table 2
Exploratory factor analysis of the SRA-74, with the prevalence rates for each individual item.

Factor	Items	Factor loading	Prevalence
1. Appetite	19. I have an increased appetite	1.098	49%
	32. I am hungry more often	0.689	47%
2. Slowed down	16. I think more slowly	0.596	44%
	13. I react more slowly	0.554	52%
	50. I move more slowly	0.431	44%
	26. I can't remember well	0.419	45%
	65. I have more trouble concentrating	0.329	42%
3. Recovery cognition	03. I can think more clearly	0.761	77%
	04. I feel calmer	0.711	66%
	02. I am more stable	0.666	63%
	05. I am able to follow conversations better	0.662	78%
	01. I feel more like myself	0.631	79%
	11. My thoughts are calmer	0.537	74%
	12. I feel less confused	*0.414	72%
	35. I have more control over my thoughts	0.304	80%
4. Weight gain	30. I am less irritable	<0.30	85%
	46. I have gained too much weight	−0.958	55%
	60. My weight has increased	−0.898	60%
5. Recovery social	66. I am less fit	<0.30	48%
	63. Dealing with others is easier	−0.871	86%
	61. I dare to make contact with people again	−0.803	86%
	64. I have more interest in my surroundings	−0.709	86%
6. Sexual problems	71. I am better at holding conversations	−0.603	88%
	62. I feel physically healthier	−0.377	88%
	70. My sex drive is too low	−0.884	31%
	17. My sex drive has decreased	−0.791	42%
	55. It is more difficult for me to have an orgasm	−0.715	28%
7. Increased sleep	10. I sleep too much	0.784	49%
	51. I need more sleep	0.715	62%
	58. I have more difficulty waking up	0.622	48%
	72. I can sleep better	−0.412	71%
	25. I feel more drowsy	0.338	55%
8. EPS	24. I get mentally tired more quickly	<0.30	52%
	41. My muscles are more tense	0.798	31%
	48. My muscles are more stiff	0.689	36%
	54. I have more tremors	0.385	27%
	56. I have more trouble sitting still	<0.30	30%
9. Social withdrawal	67. I have a dry mouth more often	<0.30	36%
	68. I have less energy for socializing	0.715	38%
	23. I am less interested in socializing	0.590	34%
	36. I have more difficulty keeping up with conversations	0.475	37%
	37. I am less spontaneous	0.389	38%
10. Flattened affect	43. I get physically tired more easily	0.330	57%
	73. I am more detached	<0.30	30%
	09. My emotions are dull	0.866	54%
	14. My emotions are too dull	0.800	44%
	40. I am less emotional	0.567	42%
11. Recovery psychosis	69. My thoughts are subdued	<0.30	53%
	07. My mind is blank more often	<0.30	36%
	22. I am less creative	<0.30	40%
	49. I am less psychotic	0.652	60%
	52. I hear fewer voices	0.458	73%
12. Recovery attention	18. I am less anxious	0.307	80%
	28. I am more active	0.594	90%
	29. My memory has improved	0.528	92%
	27. I can concentrate better	*0.471	87%
	34. I feel happier	0.463	89%
13. Miscellaneous	33. My feelings have returned	0.320	93%
	20. I am more confident	<0.30	84%
	38. My sex drive has increased	<0.30	9%
	21. I black-out more often	0.307	20%
	42. I have increased salivation	<0.30	36%
	44. I am dizzy more often	<0.30	31%
	57. My vision is more blurred	<0.30	30%
	59. I am nauseous more often	<0.30	18%
45. I am constipated more often	<0.30	20%	
53. I leak urine more often	<0.30	20%	
47. I perspire more	<0.30	33%	

Table 2 (continued)

Factor	Items	Factor loading	Prevalence
14. Depressive	06. I feel more depressed	−0.584	20%
	15. I feel down	−0.578	33%
	08. I feel more restless	−0.450	23%
	39. I am more irritable	−0.301	20%
	31. I get psychotic symptoms	<0.30	11%
Female only	74. I menstruate less often		19%

Generalized Least Squares factor analysis with Direct Oblimin Rotation identified 14 latent factors. Cross-loadings of item #12 on factor 11 (0.384) and item #27 on factor 3 (0.327) were marked by an asterisk (*). Item #74 was for females only and therefore not included in factor analysis. EPS = Extrapyramidal motor symptoms.

What is the place of the SRA-34 in comparison with existing instruments? The LUNTERS (Day et al., 1995) and GASS (Waddell and Taylor, 2008) comprise detailed physical side effects. The SRA-34 not only contains important physical side effects, but also measures psychological effects of antipsychotics, such as emotional, cognitive and social functioning. The SWN and PETIT questionnaire typically cover some of the latter psychological effects (e.g. My thinking is difficult and slow), as well as some desired subjective experiences with antipsychotics similar to the SRA-34 (e.g. I find it easy to keep in touch with people around me) (Naber et al., 2001; Voruganti and Awad, 2002), but no physical side effects. The SRA-34 can be used for a quick yet comprehensive evaluation of the patients' experiences with antipsychotics. Experiences in response to new medication can be evaluated by assessment of the SRA-34 before and after switching antipsychotics in daily clinical practice or clinical trials. Completing the SRA-34 should take a patient on average 5–10 min, about half the time needed to complete the SRA-74 (Wolters et al., 2006). Since we did not change the wording or add new items, we assume that the test-retest reliability of the SRA-34 is comparable with the original version. A next step in the development of the SRA-34 would be to test the feasibility in clinical practice and to validate the questionnaire by evaluating the association with clinical outcomes, e.g. whether (un)desired effects are predictive for antipsychotic non-adherence, switching, relapse psychosis or hospitalization.

A strong point of the current study is that our analysis was based on a large sample of patients with psychotic disorders using a wide range of antipsychotics and doses. Although we had a high response rate, responding patients were slightly younger and more likely to be male and treated as outpatients. This would suggest that some patient groups such as elderly and inpatients had more difficulties in completing the questionnaire. However, we believe that the exclusion of these patients did not lead to major bias of the results, as the current cohort appears to be representative for mental health practice with similar prescribing patterns and exploratory factor analysis is a robust method, especially in large samples. By reducing the SRA to 34 items, we hope that all patients will be able to complete the SRA. An inherent limitation of the current study is that patients may have difficulties in distinguishing antipsychotic effects from symptoms associated with the illness or effects of co-medication. This remains an important and challenging question for clinicians in daily practice. But because of the large sample size, we believe it unlikely that this introduced systematic bias in our analysis. Another possible limitation of the study was that we applied exploratory factor analysis to a three-point scale (SRA-74), which could lead to an overestimation of the number of factors (Woods, 2002). We minimized this risk by selecting the Generalized Least Squares method of EFA. Furthermore, the visual representation of the latent structure (by means of similarity analysis based on mutual information) enabled us to detect artificial correlations.

In the clinical situation, the SRA-34 can be used to discuss the balance between desired and undesired effects of antipsychotics with the

74	Total number of SRA items
-23	Eliminated non-factorable items (exploratory factor analysis)
12	All loadings <0.3
2	Cross-loadings of >0.30
8	Main factor loading <0.50
1	Responded by females only
11	Retained non-factorable items because of clinical relevance (expert panel)
-28	Eliminated factorable items considered redundant (expert panel)
14	ambiguous content
7	non-specific content
4	evoking socially desired responses
3	dependent on external factors
34	Number of items of shorter version of SRA

Fig. 1. Overview of SRA items eliminated in sequential steps of the analysis.

patient. In line with previous studies, our patients were rather satisfied with their antipsychotics (Hofer et al., 2002; Freudenreich et al., 2004). Asking patients to recall the beneficial effects of antipsychotics (e.g. from treatment-free periods) may support treatment adherence in an indirect manner (Tranulis et al., 2011). Insight in the patients' appraisal of antipsychotics may help the clinician to understand the patients' attitude towards medication and reinforces the process of shared decision making (Goff et al., 2010). Monitoring desired and undesired effects could thereby prevent relapse psychosis (Valenstein et al., 2002; Weiden et al., 2004) and an increase in costs associated (Gilmer et al., 2004). To conclude, we developed a quick and comprehensive tool to assess desired and undesired effects attributed to antipsychotics, feasible for use in routine clinical practice and clinical trials.

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Contributors

All authors contributed to the design of the study and have approved the final manuscript. Authors Irene M. Lako and Edith J. Liemburg analyzed the data. Irene M. Lako wrote the first draft of the manuscript.

Conflict of interest statement

All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2013.02.027>.

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