

# Relationship between neuroleptic dosage and subjective cognitive dysfunction in schizophrenic patients treated with either conventional or atypical neuroleptic medication

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Previous research has suggested that high doses of conventional neuroleptics may induce neurocognitive deficits when assessed with standard tasks. However, little is known about the effects of high doses of neuroleptics (conventional or atypical) on subjective cognitive dysfunction. Recent research stresses the putative importance of self-reported cognitive deficits for both symptomatic outcome and medication compliance. The aim of the present study was to investigate the impact of neuroleptic medication on subjective cognition in patients treated with either conventional or atypical agents (clozapine, risperidone, olanzapine). Patients were asked to endorse the items of a questionnaire entitled 'Subjective Well-Being under Neuroleptic Treatment' prior to discharge. Subjective impairment, as assessed with the subscale 'mental functioning', was significantly correlated with greater conventional neuroleptic dosage after controlling for psychopathology ( $P < 0.05$ ). The difference between patients medicated with higher doses of conventional neuroleptics and those with lower doses was highly significant ( $P < 0.001$ ). In contrast, higher atypical neuroleptic doses were not associated with impairment. Int Clin Psychopharmacol 17:41–44 © 2002 Lippincott Williams & Wilkins

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## INTRODUCTION

Since the early work of Kraepelin and Bleuler, neurocognitive deficits have been considered of major pathogenetic importance for the emergence of schizophrenia. However, while an extensive body of research indicates that schizophrenic patients are impaired on a wide range of cognitive functions, no deficit pattern specific to schizophrenic psychopathology has yet been established (Moritz *et al.*, 2001a).

Neurocognitive deficits are most often indexed using so-called objective measures (e.g. the Wisconsin card sorting test). A somewhat neglected aspect of

neurocognition in schizophrenia research refers to subjective assessment. Recent research suggests that the assessment of subjective deficits bears special potential importance for predicting symptomatic outcome and medication compliance. Moritz *et al.* (2000) report that subjective cognitive dysfunction, as assessed by the Frankfurt Complaint Questionnaire (FCQ), predicted symptomatic outcome in first-episode schizophrenic patients. Furthermore, it has been suggested that subjective cognitive dysfunction under neuroleptics may have a negative impact on medication compliance (Moritz *et al.*, 1999). For example, Naber (1995) found that high scores in a scale measuring

subjective cognitive, physical and other side-effects under neuroleptic treatment were correlated with later medication non-compliance.

The finding that atypical agents, such as olanzapine, risperidone and clozapine, ameliorate some primary objective cognitive deficits is frequently reported (for review, see Keefe *et al.*, 1999; Moritz *et al.*, 2001b). There is some evidence that this effect may also transfer to subjective cognitive deficits. It should be noted in this context that the cognitive dysfunction perceived by schizophrenic patients themselves has been shown to be correlated with objective neurocognitive measures (Cuesta *et al.*, 1996). Naber *et al.* (2001) found that patients treated with olanzapine showed greater improvement than those either taking risperidone or clozapine over the course of inpatient treatment. In addition, Morgner (1992) has shown that clozapine is superior to haloperidol across several subjective cognitive and motor aspects.

Another issue related to neuroleptic treatment, which is the topic of the present study, deals with the impact of neuroleptic dosage on neurocognition. Sweeney *et al.* (1991) demonstrated that conventional neuroleptic dosage and benztropine dosage were significantly correlated with several aspects of objective neurocognitive functioning; see also Spohn *et al.* (1985). Our group (Krausz *et al.*, 2000) has reported evidence that conventional neuroleptic dosage was significantly correlated with subjective cognitive deficits as assessed by the FCQ.

The aim of the present study was to investigate whether atypical (clozapine, risperidone, olanzapine) and conventional agents have similar dose-related effects on self-report neurocognitive functioning. It is hypothesized that patients receiving higher doses of conventional antipsychotics display decreased neurocognitive well-being.

## METHODS

### Participants

A total of 207 schizophrenic patients were enrolled in the study. Recruitment was carried out in two different clinical settings. Patients on risperidone ( $n=26$ ) and olanzapine ( $n=40$ ) took part in a medication study with random medication assignment following a wash-out period of at least 3 days, whereas patients on clozapine ( $n=35$ ) and conventional neuroleptics ( $n=106$ ; predominantly haloperidole and flupenthixole) were assessed in a naturalistic clinical design. Informed consent was obtained from all patients. Patients were naive to the hypotheses of the study. Data was collected shortly before discharge. All

patients met DSM-IV criteria for schizophrenia or schizophreniform disorder. Diagnoses were determined by experienced clinicians. Psychopathology was further assessed using the Positive and Negative Syndrome Scale (PANSS) following a semi-structured interview (SCI-PANSS). Patients with severe neurological illness, other axis 1 diagnoses and substance abuse were excluded from the samples. For the purpose of this study, doctors-in-charge were not recommended any dose ranges. No concomitant drugs were prescribed except for the occasional application of benzodiazepines in the groups treated with atypicals. Sociodemographic and psychopathological characteristics of the sample are shown in Table 1.

### Questionnaire

Patients were administered the short form of a questionnaire entitled 'Subjective Well-Being under Neuroleptic Treatment' (SWN-S; Naber, 1995; Naber *et al.*, 2001). The SWN-S is a 20-item scale that has been designed to assess subjective antipsychotic side-effects. It has been translated into several languages and is widely used in clinical trials to assess various domains of side-effects. Its five subscales index the following functions: mental functioning, self-control, emotional regulation, physical functioning and social integration. Items are to be endorsed on a six-point Likert scale. For the present analysis, only items from the subscale 'mental functioning' were submitted for analysis (example: 'my thinking is difficult and slow'). Higher scores in the SWN correspond to greater well-being.

## RESULTS

Table 1 displays the sociodemographic and psychopathological background variables of the four samples. Since no admission scores were determined for patients and groups largely differed regarding several background variables (Table 1), SWN-differences at discharge do not allow for differential interpretation. Except for overall psychopathology ( $r=-0.29$ ,  $P<0.001$ ), no other psychopathological or sociodemographic variable (e.g. gender, age, length of illness) correlated with the SWN subscale 'mental functioning'.

Partial correlations controlling for psychopathology (overall PANSS symptoms) revealed a significant negative correlation between dosage of conventional neuroleptics and 'mental functioning' ( $r=-0.21$ ,  $P=0.038$ ). No significant relationships emerged for clozapine ( $r=0.22$ ) and olanzapine ( $r=-0.10$ ). In the

Table 1. Sociodemographic and psychopathological characteristics of the samples<sup>a</sup>

|   | Clozapine ( <i>n</i> =35) | Risperidone ( <i>n</i> =26) | Olanzapine ( <i>n</i> =40) | Typical neuroleptics ( <i>n</i> =106) |
|---|---------------------------|-----------------------------|----------------------------|---------------------------------------|
| Sociodemographic variables  |                           |                             |                            |                                       |
| Age (SD) (years)  | 37.4 (12.5)               | 39.3 (17.6)                 | 29.4 (7.8)                 | 37.2 (12.0)                           |
| Gender (male/female)  | 22/13                     | 8/18                        | 24/16                      | 46/60                                 |
| Treatment variables   |                           |                             |                            |                                       |
| Dosage (range) in mg (atypical agents) or chlorpromazine equivalent doses | 229.6 (145.9) (12.5–600)  | 4.2 (1.8) (1–8)             | 12.5 (4.9) (2–20)          | 235.0 (203.8) (14–900)                |
| Length of current hospitalization (days)                                  | 58.1 (32.6)               | 27.4 (19.7)                 | 35.9 (19.1)                | 57.7 (42.2)                           |
| Length of illness (years)   | 8.8 (8.3)                 | 6.7 (8.0)                   | 4.3 (4.5)                  | 9.3 (8.1)                             |
| PANSS positive discharge  | 13.8 (5.3)                | 14.7 (6.2)                  | 14.2 (3.7)                 | 13.6 (5.8)                            |
| PANSS negative discharge  | 19.2 (8.4)                | 18.6 (7.7)                  | 16.8 (5.0)                 | 20.5 (8.7)                            |
| PANSS global discharge  | 33.9 (12.1)               | 36.6 (11.6)                 | 34.9 (11.5)                | 33.2 (10.5)                           |
| SWN-mental functioning discharge  | 16.1 (4.0)                | 16.4 (4.1)                  | 18.1 (3.1)                 | 16.2 (4.7)                            |

<sup>a</sup>Due to differences in the clinical setting, no group comparisons were conducted.

case of risperidone, a significant positive partial correlation was detected ( $r=0.49$ ,  $P=0.015$ ).

Since the primary aim of the study was to investigate the impact of higher doses of neuroleptics on subjective cognitive functioning, samples were split into high and low dosage groups. The high dosage groups were defined as typical agents: at least 400 mg chlorpromazine; equivalent doses: risperidone, at least 6 mg; clozapine, at least 400 mg; olanzapine, at least 15 mg. No significant differences between low and high dosage patients emerged for atypical agents (all  $P>0.2$ ). Patients receiving high typical doses ( $n=21$ ) showed 13.28 (SD 4.5) points on the SWN-subscale relative to 16.91 (SD 4.5) in the low dosage group ( $n=81$ ;  $t=3.31$ ;  $P<0.001$ ). The difference remained highly significant after controlling for overall PANSS symptoms in a subsequent ANCOVA.

## DISCUSSION

The focus of the present study was to explore the impact of neuroleptic dosage on subjective cognitive deficits as indexed with the SWN subscale 'mental functioning'. The findings replicate and extend previous studies reporting cognitive decline under higher doses of conventional neuroleptics (Krausz *et al.*, 2000; Sweeney *et al.*, 1991). Small but significant inverse correlations emerged between conventional neuroleptic dosage and cognitive dysfunction as assessed with the SWN. When the sample treated with conventional neuroleptics was divided into high and low dosage patients, a highly significant between-group difference was obtained regarding SWN scores. With respect to atypical neuroleptic agents, a different picture

emerged. For risperidone and clozapine, positive correlations were measured. However, no group differences occurred after division into low and high dosage groups.

The present results indicate that when high neuroleptic doses are clinically necessary, atypical rather than conventional neuroleptics should be prescribed because medication-induced deficits are more likely to appear under conventional agents. It is also important to note that anti-Parkinson by-medication, which is more often prescribed in conventional than atypical neuroleptics, has also been found to induce objective and subjective deficits (Sweeney *et al.*, 1991; Krausz *et al.*, 1999).

More research is needed to confirm the present results before any definite conclusions can be drawn. First, only a restricted set of cognitive functions was assessed that may best be referred to as subjective 'mental fluency'. Second, the dose range in patients medicated with atypical agents was rather narrow. It cannot be entirely ruled out that higher doses of atypical neuroleptics may lead to different results. Therefore, our conclusions are limited to the dose ranges investigated. Subsequent research should investigate if the present findings hold true for objective tasks, other atypical agents, wider dose ranges and subjective rating scales that cover a greater number of cognitive symptoms.

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## REFERENCES

- Cuesta MJ (1996) Abnormal subjective experiences in schizophrenia: its relationships with neuropsychological disturbances and frontal signs. *Eur Arch Psychiatry Clin Neurosci* **246**:101–105.
- Keefe RSE, Silva SG, Perkins DO, Lieberman JA (1999) The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophr Bull* **25**:201–222.
- Krausz M, Moritz S, Naber D, Lambert M, Andresen B (1999) Neuroleptic-induced extrapyramidal symptoms are accompanied by cognitive dysfunction in schizophrenia. *Eur Psychiatry* **14**:84–88.
- Krausz M, Moritz S, Lambert M, Naber D (2000) Dosage of conventional neuroleptic medication and subjective cognitive functioning in schizophrenia. *Int Clin Psychopharmacol* **15**:77–81.
- Morgner J (1992) Die Therapie schizophrener Ziel- und Basissymptome mit Clozapin (Leponex<sup>®</sup>). In: *Clozapin. Pharmakologie und Klinik eines atypischen Neuroleptikums: Eine kritische Bestandsaufnahme* (Naber D, Müller-Spahn F, eds), Stuttgart: Schattauer, pp. 43–50.
- Moritz S, Naber D, Krausz M, Lambert M, Andresen B (1999) Neurokognitive Veränderungen in der Behandlung schizophrener Patienten mit Clozapin. In: *Clozapin. Pharmakologie und Klinik eines atypischen Neuroleptikums* (Naber D, Müller-Spahn F, eds), Berlin: Springer, pp. 90–108.
- Moritz S, Krausz M, Gottwalz E, Lambert M, Perro C, Ganzer S, Naber D (2000) Cognitive dysfunction at baseline predicts symptomatic one-year outcome in first-episode schizophrenics. *Psychopathology* **33**:48–51.
- Moritz S, Kloss M, Jahn H, Hand I, Haasen C, Krausz M (2001a) Executive functioning in obsessive-compulsive disorder, unipolar depression and schizophrenia. *Arch Clin Neuropsychology*, in press.
- Moritz S, Naber D, Lambert M (2001b) Neurocognition under atypical and conventional neuroleptics. In: *Atypical Neuroleptics* (Naber D, Lambert M, Krausz M, eds), in press.
- Naber D (1995) 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* **10** (Suppl. 3):133–138.
- Naber D, Moritz S, Lambert M, Pajonk F, Holzbach R, Mass R, Andresen B (2001) Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. *Schizophr Res* **50**:81–90.
- Spohn HE, Coyne L, Lacoursiere R, Mazur D, Hayes K (1985) Relation of neuroleptic dose and tardive dyskinesia to attention, information-processing, and psychophysiology in medicated schizophrenics. *Arch Gen Psychiatry* **42**:849–859.
- Sweeney JA, Keilp JG, Haas GL, Hill J, Weiden PJ (1991) Relationships between medication treatments and neuropsychological test performance in schizophrenia. *Psychiatry Res* **37**:297–308.