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Higher than recommended dosages of antipsychotics in male patients with schizophrenia are associated with increased depression but no major neurocognitive side effects: Results of a cross-sectional pilot naturalistic study

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ABSTRACT

Introduction: The current small pilot naturalistic cross-sectional study assesses whether higher dosages of antipsychotics are related to a satisfactory outcome concerning symptoms of schizophrenia but also to a worse outcome in terms of adverse events and neurocognitive function.
Material and methods: 41 male stabilized hospitalized schizophrenic patients were assessed by PANSS, Calgary Depression Rating Scale, UKU and Simpson-Angus Scale and a battery of neurocognitive tests. Medication and dosage was prescribed according to clinical judgement of the therapist.
Results: Clinical variables and adverse events did not differ between patients in the recommended vs high dosage groups. Higher dosage correlated with depressive symptoms but there was no correlation with neurocognitive measures except for impaired concentration.
Discussion: Results suggest that it is possible to achieve a good clinical response in refractory patients by exceeding recommended antipsychotic dosages at the price of depression and possible mild isolated concentration deficits but not other neurocognitive or extrapyramidal adverse events. Currently clinicians prefer first-generation antipsychotics when high dosages are prescribed, but considering the more favorable adverse effects profile of newer agents, it is important to study higher dosages of these agents and to test whether they should be preferably given when high dosages are necessary.

1. Introduction

In the era of evidence based psychiatry, randomized controlled trials (RCTs) constitute the backbone of clinical medical research. However clinicians are somewhat skeptical of whether the results of this kind of studies can be carried to the everyday clinical practice. RCTs include only highly selected patients and utilize a treatment methodology based on randomization, which is very far away from the everyday clinical practice and also from the concept the average clinician has concerning treatment choice.

Reservation is especially present among psychiatrists and it is reflected in the low penetration of research findings and treatment guidelines in clinical practice. Even with these highly selected patients, the effect size of antipsychotics is medium or low (approximately 0.40 against positive symptoms) while the drop-out rate is high (24–40%) (Schalkwijk et al., 2014).

Anecdotal reports suggest that various treatments behave in a different way in RCTs and in the real world clinical practice and both the therapeutic effect and the adverse events profile are quite different between these two conditions.

Apart from the different quality of the patients, also the treatment practice is completely different. The predominant practice is to 'optimize' treatment through a series of trial and error, on the basis of

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response, adverse events and the utilization of a number of variables which are almost never taken into consideration in RCTs, such as the detailed personal and family history, elements of the clinical picture, personal preference of the patient and/or his family etc. In terms of 'hard science', most of these variables are of doubtful or unknown utility and their precise study would require the recruitment of so large numbers of patients in so complex and expensive treatment designs that it is impractical to carry out.

An additional issue is that recently it has been proposed that patients with schizophrenia should be classified into stages (Agius et al., 2014; Cosci and Fava, 2013; Fava and Kellner, 1993; McGorry, 2007, 2010a, b; McGorry et al., 2006, 2010, 2007; Vieta et al., 2011; Yung and McGorry, 1996, 2007) and maybe no treatment should be given in those not expected to respond in a satisfactory way (Davidson, 2014). This poses again the issue of adequate dosage and overall outcome, before one decides to shift into palliative care only.

The current study is a small pilot naturalistic cross-sectional study which aimed to investigate whether higher dosages of antipsychotics are related to a satisfactory outcome concerning the symptoms of schizophrenia but also to a worse outcome in terms of adverse events and neurocognitive function. The data came from stabilized patients with schizophrenia who were treated according to the 'optimization' method of the usual everyday clinical practice.

2. Material and methods

2.1. Study population

The study included a convenient sample of 41 male hospitalized patients suffering from schizophrenia according to DSM-IV-TR. The characteristics of these patients are shown in Tables 1 and 2. According to Andreasen et al. (2005) remission criteria most of the patients could be considered as in partial remission and only 5 (12.2%) in full remission, which is lower than the percentage expected in RCTs (27–53%) (Leucht, 2014). However individual criteria are satisfied by a significantly higher percentage (Table 2).

All patients were acutely hospitalized in private psychiatric clinics and at the time of assessment were stabilized and able to cope with all the study protocol. They were consecutive cases and all belonged to the undifferentiated subtype. All were physically healthy. All gave informed consent and the protocol received approval by the University's Ethics Committee.

2.2. Clinical assessment and diagnosis

The diagnosis was made according to DSM-IV-TR criteria on the basis of a semi structured interview based on the Schedules for Clinical Assessment in Neuropsychiatry version 2.0 (SCAN v 2.0) (Wing et al., 1990). The final diagnosis was put after consensus between KNF and MS

2.3. Psychometric assessment

The psychometric assessment was performed by a qualified psychiatrist (MS) and included the Positive and Negative Symptoms Scale (PANSS) and its subscales (Kay et al., 1989), and the Calgary Depression Rating Scale (CDRS) (Addington et al., 1992; Addington et al., 1990). The side-effects of medications were assessed with the UKU (Lingjaerde et al., 1987) while the Simpson-Angus rating scale was used specifically for the assessment of extrapyramidal side effects (Simpson and Angus, 1970).

2.4. Neuropsychological assessment

The neuropsychological assessment was performed by a qualified psychologist (KM) and included the following measurements:

Table 1
Descriptive statistics of the study sample of male schizophrenic patients.

	Total sample (N = 41)		Dosage >800 mg/day in chlorpromazine equivalents (N = 30)		Dosage ≤800 mg/day in chlorpromazine equivalents (N = 11)		p
	Mean	Std. dev.	Mean	Std. dev.	Mean	Std. dev.	
Age	44.24	12.91	44.63	12.39	43.18	14.83	0.754
Body Mass Index	26.79	3.95	26.55	4.07	27.45	3.72	0.523
Number of oral antipsychotics	**1.53**	**0.74**	**1.70**	**0.75**	**1.09**	**0.54**	**0.018**
Chlorpromazine equivalents	**1766.46**	**1110.31**	**2192.58**	**997.53**	**604.32**	**122.90**	**0.000**
Biperiden dosage	5.54	1.99	5.72	2.03	4.83	1.83	0.337
PANSS							
PANSS total	63.17	12.29	62.11	11.77	65.07	14.35	0.442
PANSS-P	15.24	4.45	14.55	4.38	16.20	5.33	0.252
PANSS-N	19.61	5.57	19.42	5.63	20.20	5.28	0.647
PANSS-GP	28.32	6.53	28.13	5.94	28.67	8.43	0.795
PANSS-EC	7.24	3.18	6.89	2.66	7.60	3.76	0.444
CDRS	1.76	2.96	2.11	3.05	0.80	2.34	0.142
UKU	8.47	4.63	8.46	4.32	7.07	4.56	0.310
SAS	2.76	2.58	2.58	2.62	1.73	2.09	0.269
Neurocognitive tests							
RLT errors of omission	76.32	43.09	80.00	40.58	73.33	45.77	0.611
RLT errors of commission	67.16	46.21	62.11	47.14	80.13	41.13	0.205
Digits backward	2.55	2.15	2.46	2.11	2.40	2.13	0.931
Logic memory	5.21	4.38	5.43	4.47	5.53	3.34	0.936
Total words from letters	7.95	5.50	8.87	7.98	7.38	6.97	0.554
Total words for groups	24.08	6.77	23.95	7.48	24.38	5.27	0.847
SGST							
SGST-DCI	567.59	172.99	569.97	170.18	651.21	135.78	0.116
SGST-DFI	454.97	132.37	467.35	133.89	479.14	135.40	0.781
SCPT							
SCPT-DcI	311.10	162.85	343.24	164.57	337.00	175.93	0.903
SCPT-DfI	752.37	177.90	766.34	181.88	813.73	159.94	0.382
SCPT-CiI	194.98	58.46	204.50	64.40	194.87	48.43	0.603
SCCT							
SCCT-DcI	285.15	180.35	299.61	176.73	308.60	177.52	0.868
SCCT-DfI	495.88	182.03	500.66	179.50	530.47	173.93	0.585
SCCT-CiI	92.68	26.37	92.11	27.33	100.00	0.00	0.271
Draw a Clock (Mendez method)	15.76	5.30	16.05	5.37	16.93	3.90	0.567
Rey-Osterrieth Figure full score	20.95	8.77	0.47	0.51	0.67	0.49	0.212

Significant values ($p < 0.05$) are shown in bold. PANSS: Positive and Negative Symptoms Scale, PANSS-P: PANSS Positive Scale, PANSS-N: PANSS Negative Scale, PANSS-GP: PANSS General Psychopathology Scale, PANSS-EC: PANSS Excited Component, CDRS: Calgary Depression Rating Scale, UKU: UKU Side Effects Rating Scale, SAS: Simpson-Angus Scale, RLT: Random Letter Test, SGST: Standardized Graphic Sequence Test, SGST-DcI: SGST Deficit Index, SGST-DFI: SGST Deformation Index, SCPT: Standardized Copy of Pentagons Test, SCPT-DcI: SCPT Deficit Index, SCPT-DfI: SCPT Deformation Index, SCPT-CiI: SPT Closing-In Index, SCCT: Standardized Copy of a Cube Test, SCCT-DcI: SCCT Deficit Index, SCCT-DfI: SCCT Deformation Index, SCCT-CiI: SCCT Closing-In Index.

The Random Letter Test (*RLT*) for the assessment of attention and vigilance (Fountoulakis et al., 2008; Strub and Black, 1989).

Digits backward: the maximum number of correctly recalled digits was used.

Logic memory: recall of the elements from a short story (27 elements).