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ORIGINAL ARTICLE

Evaluation of Defined Daily Dose, percentage of British National Formulary maximum and chlorpromazine equivalents in antipsychotic drug utilization

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KEYWORDS

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Abstract *Objective:* The present study was carried out to investigate and compare the three methods for calculating total antipsychotic dose among outpatients with schizophrenia attending primary psychiatric health care centers. The three methods were: Defined Daily Doses (DDDs), chlorpromazine equivalents (CPZeq) and percentages of the British National Formulary (BNF) maximum.

Methodology: Antipsychotic drug dosing data for 250 patients with schizophrenia were investigated by calculating Spearman's rank correlation coefficients. Factors associated with antipsychotic dose, expressed as DDDs, CPZeq and percentages of the BNF maximum recommended daily dose, were investigated by means of linear regression analysis.

Results: Spearman's correlation showed that there is a significant relationship between all pairs of the three dosing methods. In all three methods, coherence was strongest when dealing with first generation antipsychotics (FGA). Linear regression analyses showed a high degree of coherence

Abbreviations: %BNFmax, percentage of British National Formulary maximum; CPZeq, chlorpromazine equivalents; DDD, Defined Daily Dose (DDD); FGA, first generation antipsychotics; SGA, second generation antipsychotics.

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between antipsychotic doses expressed as DDDs, CPZeq and percentages of the BNF maximum recommended daily dose.

Conclusion: All three tested methods are reliable and coherent for calculating antipsychotic dosing.

1. Introduction

Drug utilization studies are important in detecting drug related-problems and in assessing conformance of clinical practice to international recommendations. Such studies are not meant to find blame, but to implement regulations, and cost-effective treatment protocols. Schizophrenia is a devastating mental illness that affects around 0.3–0.7% of people at some point in their life, or 24 million people worldwide as in the World Health Organization (WHO) report 2011 (WHO, 2011). The introduction of chlorpromazine to clinical use in early 1950s and subsequent antipsychotic agents have revolutionized the treatment of schizophrenia and has led to an increase in prescribing of this category of drugs for various mental disorders. The interest in antipsychotic agents stimulated researchers in several countries to publish data regarding antipsychotic drug utilization (Alonso et al., 2004; Piparva et al., 2011). Such studies focus not only on the pattern of antipsychotic prescribing but also on the appropriateness of antipsychotic dose which is mentioned in international guidelines (Buchanan et al., 2009; NICE, 2011). Calculation of the dose of antipsychotic agents has been a subject for debate. The three methods suggested to calculate the antipsychotic dose are: Chlorpromazine equivalents (CPZeq), percentage of British National Formulary (BNF) maximum, and Defined Daily Dose (DDD) (Nose et al., 2008). Few studies have been carried out to investigate the coherence between these methods. A study by Nose et al. showed a high degree of coherence between antipsychotic doses expressed as DDDs, CPZeq and percentage of BNF maximum recommended daily dose and that the DDD system is a reliable tool for standardizing antipsychotic doses in drug utilization research (Nose et al., 2008). However Rijcken et al. found a great discrepancy between CPZeq and DDD methods of comparing antipsychotic drug doses and recommended further research in this regard (Rijcken et al., 2003).

Studies comparing the various methods for calculation of antipsychotic dosing are few. Therefore, this study was carried out to further investigate and compare the three methods for calculating total antipsychotic dose among outpatients with schizophrenia attending primary psychiatric health care centers.

2. Methods

The data for the present study were based on a cross sectional study conducted between August 2011 and February 2012 to investigate the prescribing pattern of antipsychotics in primary healthcare centers in northern West-Bank, Palestine. The Palestinian territories, where the study took place, comprise the West Bank, Gaza Strip and East Jerusalem. This study was carried out at four governmental primary psychiatric healthcare centers located in Nablus, Tulkaram, Jenin and Qalqilia in northern West-Bank, Palestine. Patients who fulfilled the following criteria were considered for the study: (1) their age was above 16 years, (2) they were diagnosed with schizophrenia as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), (3) they had not been suffering from an acute attack of psychiatric illness during the past year, and (4) their drug regimen had not been changed in the past 6 months as evident from their medical files. Patients who had the following characteristics were excluded from the study: (1) newly diagnosed patients and (2) patients who were not on any antipsychotic medication. The final sample collected during the study period was 250 patients. We developed data collection forms that covered the following areas: socio-demographic variables, psychiatric history, antipsychotic medication currently being used, and history of psychiatric hospitalization. Focus group discussions were continuously held between the research team to maintain rationale of the data collection process. Regular evaluations took place throughout the abstraction period to identify any problems in the data collection, the interpretation of definitions, and the application of study criteria. Before commencing data analysis, an extensive series of checks were performed for data consistency, proper sequences of data, and an evaluation of missing or incomplete data. The data collection form was modified by the principle researchers and the modified version was reviewed by experts to ensure content and construct validity. Data from the pre-test evaluation were not included in the final analysis. Approval to perform the study was obtained from the Palestinian Ministry of Health, the College of Graduate Studies at An-Najah National University and the Institutional Review Boards (IRB) committee at An-Najah National University.

2.1. Tested variables

2.1.1. Chlorpromazine dose equivalents (CPZeq)

The CPZeq is a measure of the relative antipsychotic potencies of neuroleptics. They are generally expressed as a ratio, relative to the arbitrary value of 1, which corresponds to the antipsychotic effects of chlorpromazine. The daily dose of antipsychotic medication prescribed to each patient was converted into milligram equivalents of chlorpromazine according to conversion factors derived from the literature (Davis, 1976; Rey et al., 1989; Woods, 2003; Xiang et al., 2008; Joseph et al., 2011). Total CPZeq was constructed by calculating a total daily dose of each antipsychotic listed in the medical file. Then each converted antipsychotic-specific CPZeq amount is added to arrive at a total dose. This CPZ equivalency is most often based on the antidopaminergic action and in general does not take into account the influence of antipsychotics on serotonergic, histaminergic, cholinergic, and adrenergic receptors. Generally, CPZ-equivalent values per drug are ambiguous in the literature (Rey et al., 1989). The origin of the used equivalency value per study is in general quite opaque. Most likely, researchers base their equivalencies on pharmacologic drug registration studies and other available literature. As a result of this nontransparency,

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an up to threefold variation in CPZ-equivalent values has been reported in the literature. For example, the CPZ-equivalent for haloperidol varies from 40 to 60 times more potent than CPZ (Rey et al., 1989). The ambiguity in CPZeq becomes more important when dealing with second generation antipsychotics (SGA) because there are evidence that the maximum efficacy of this drug class occurs at 70–80% of the dopamine receptor occupancy and these levels can be achieved at doses much lower than have been previously thought necessary (McEvoy et al., 1991; Stone et al., 1995).

2.1.2. Percentage of BNF maximum

To calculate a total daily prescribed antipsychotic dose as a percentage of the maximum BNF dose, we determined the percentage of BNF maximum dosage for each antipsychotic that is used, and then we summed the percentages (Yorston, 2000). For example, for a person prescribed clozapine 400 mg a day and oral haloperidol 5 mg three times a day, the respective percentages would be 44% and 50%, giving a total antipsychotic prescribed dosage of 94% of the BNF maximum. The BNF is updated twice a year and maximum doses are assumingly accurate and are generally based on toxicity rather than efficacy (Yorston, 2000).

2.1.3. Defined Daily Dose (DDD)

The DDD is a theoretical unit of measurement defined as the assumed average maintenance daily dose for a drug, used for its main indication in adults (WHO, 2010). The DDD for antipsychotic agents is calculated by converting the daily doses in milligrams into multiples of the DDD by dividing the prescribed daily dose (PDD) by the DDD (PDD/DDD) (WHO, 2010). For patients who were on multiple antipsychotics, the total DDD was calculated by adding the DDD for each antipsychotic agent in a way similar to that mentioned for percentage BNF maximum.

2.2. High doses

For the purpose of this study, patients receiving percentage of BNF maximum dose >100% were considered to have a high dose. On the other hand, patients who were receiving >600 CPZeq were considered to have a high dose. This upper limit of CPZeq was based on international recommendations for maintenance dose between 300 and 600 CPZeq (Buchanan et al., 2009). For DDDs, no definition of high dose is available in the literature and therefore was dealt with as a continuous variable.

2.3. Data analysis

Descriptive statistics for all study variables were computed. These descriptive statistics included frequencies and percentages for all categorical variables in addition to means, standard deviations and ranges for all normally distributed continuous variables while median and inter quartile range (Q1–Q3) for continuous variables that were not normally distributed. Variables were tested for normality using the Kolmogorov–Smirnov test. Correlation between variables was tested using the Spearman Rho correlation test. The conventional 5% significance level was used throughout the study. Linear regression was carried out to analyze the association between each method and various independent variables. All statistical analyses were conducted using Statistical Package for Social Sciences SPSS (PASW version 18.0; IBM, Somers, NY) statistical packages for Windows.

3. Results

3.1. General descriptive statistics of the study sample

Antipsychotic medications for 250 patients were studied and analyzed. Gender distribution of the patients was: 68 (27.2%) females and 182 (72.8%) males. The mean age of the patients was 41.9 ± 11.8 years. The median duration of illness was 15 (Q1–Q3: 9–20) years. The median number of psychiatric hospitalization of the patients during their lifetime was 1 (Q1–Q3: 0–2). The total number of antipsychotic drugs used was 406 with a mean of 1.6 ± 0.7 (95% CI: 1.5–1.7) per patient. The antipsychotics were mainly from the first-generation antipsychotic (FGA) type (348, 85.7%) and the remaining were from the second generation antipsychotics (SGA). Table 1 shows the types of antipsychotic medications encountered in the study. One hundred and twenty-four clients (49.6%) were using antipsychotic monotherapy while 126 (50.4%) clients were using antipsychotic combination. The most common combination was "FGA + FGA" (78; 61.9%) followed by "FGA + FGA + FGA" (24; 19%) and "FGA + SGA" (17; 13.5%).

3.2. Correlation between DDD, CPZeq and percentage of BNF maximum

Table 2 shows a list of antipsychotic medications encountered in the study and the corresponding CPZeq, %BNF max and DDD for each medication. The relationship between the three methods is shown in Table 3. The Spearman Rho correlation between DDDs and CPZeq was 0.92 ($p < 0.01$), between DDDs and percentage of BNF maximum dose was 0.82 ($p < 0.01$) and finally between percentage of BNF maximum dose and CPZeq was 0.85 ($p > 0.01$).

Linear regression of that the factors associated with antipsychotic dosages expressed as DDDs, CPZEq and percentages of the BNF maximum recommended daily dose revealed a positive association between antipsychotic combination and duration of psychiatric illness in all three models.

Table 1 Antipsychotic medications encountered in the study.

Antipsychotic medications	
Medication	N (%)
Chlorpromazine tablet	128 (31.5)
Fluphenazine depot	125 (30.8)
Haloperidol tablet	74 (18.3)
Clozapine tablet	35 (8.6)
Olanzapine tablet	15 (3.7)
Haloperidol depot	11 (2.7)
Risperidone tablet	8 (2.0)
Trifluoperazine tablet	7 (1.7)
Zuclopenthixol depot	2 (0.5)
Thioridazine tablet	1 (0.2)
Total	406 (100)

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Table 2 Antipsychotic dosing equivalents.

Medication	CPZ equivalent dose to 100 mg CPZ[a]	100% BNF max[b]	DDD (mg)[c]
Chlorpromazine tablet	100	1000	300
Haloperidol tablet	2	30	8
Trifluoperazine tablet	5	50	20
Thioridazine tablet	100	150	300
Fluphenazine decanoate	13/4 weeks	50	1
Haloperidol decanoate	40/4 weeks	18	3.3
Clozapine tablet	100	900	300
Olanzapine tablet	4	20	10
Risperidone tablet	2	16	5
Quetiapine tablet	75	750	400

[a] Data obtained from Woods (2003); Xiang et al. (2007); Xiang et al. (2008); Buchanan et al. (2009).
[b] Joint Formulary Committee and Pharmaceutical Society of Great Britain (2010).
[c] WHO (2010).

Additionally, waist circumference was significantly associated with antipsychotic dose only when doses were expressed as CPZeq, whereas in the other two models the association was not significant (Table 4).

The impact of the type of antipsychotic regimen (FGA, SGA and FGA + SGA) on the regression line among the different dosing methods was investigated. The highest *r* square value was seen with the regression line for the FGA while that for SGA was highest for regression line between CPZeq and percentage of BNF maximum (Table 5).

According to the definition of high dose, 61 (24.4%) patients were receiving high antipsychotic dose measured using percentage of BNF maximum dose while there were 57 (22.8%) patients receiving high dose measured using CPZeq. In both methods, the depot antipsychotic medications as fluphenazine or haloperidol were associated with high dose regimens.

3.3. Antipsychotic combination and antipsychotic dose

Patients on antipsychotic combination had a mean CPZeq of 614.3 ± 267.1 (95% CI: 567.2–661.4 mg) while those on monotherapy had a mean CPZeq of 256.6 ± 127.5 (95% CI 233.9–279.3 mg) ($p < 0.01$). Categorization of CPZeq dose showed that 88 (35.2%) patients were using sub-therapeutic doses (< 300 mg CPZeq), 105 (42.2%) were using optimum dose (300–600 mg CPZeq) and 57 (22.8%) were using supra therapeutic doses (> 600 mg CPZeq). Only 7 (2.8%) clients were using supra-maximal dose (CPZeq > 1000 mg). Patients on antipsychotic combination had a mean%BNF maximum dose of 105.4 ± 48.3 (95% CI: 96.9–114) while those on monotherapy had a mean %BNF maximum dose of 44.4 ± 33.8 (95% CI: 38.4–50.4) ($p < 0.01$).

4. Discussion

The present study endorses the findings that there is coherence between DDDs, CPZeq and percentage of BNF maximum dose methods and all are reliable tools for standardizing antipsychotic doses in drug-utilization research. Our findings are in agreement and further endorse the findings of (Nose et al., 2008). The agreement in the type of antipsychotic drugs that were associated with high dose using either percentage of BNF maximum dose or CPZeq methods endorses the findings of Yortson who showed that both CPZeq and percentage of BNF maximum dose showed similar accuracy in finding high doses associated with fluphenazine or haloperidol depot (Yorston, 2000).

It should be emphasized that our conclusion is valid for outpatients who are receiving antipsychotic agents at the maintenance dose which is lower than that recommended for acute psychiatric treatment. Furthermore, our study was based on patients diagnosed with schizophrenia and were using the antipsychotics for this purpose. Therefore, our conclusion cannot

Table 3 Correlation between DDDs, %BNF max and CPZeq.

Method		%BNF max	DDDs	CPZeq
%BNF max	Correlation Coefficient	1.000	0.820**	0.853**
	Sig. (2-tailed)		0.000	0.000
	N	250	250	250
DDDs	Correlation Coefficient	0.820**	1.000	0.917**
	Sig. (2-tailed)	0.000		0.000
	N	250	250	250
CPZeq	Correlation Coefficient	0.853**	0.917**	1.000
	Sig. (2-tailed)	0.000	0.000	
	N	250	250	250

** Significant difference (*p*-Value < 0.05).

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Table 4 Linear regression of the factors associated with antipsychotic dosages expressed as DDDs, CPZeq and percentages of the BNF maximum.

Variable	Sig (P)		
	CPZeq	%BNF max	DDDs
Gender	0.837	0.772	0.892
Age	0.472	0.101	0.183
Education	0.461	0.464	0.701
Married	0.693	0.787	0.584
Occupation	0.161	0.120	0.035
Waist circumference	0.023	0.097	0.404
Duration	0.038	0.000	0.029
No. of hospitalization	0.313	0.127	0.170
Monotherapy	0.000	0.000	0.000

Table 5 Impact of the type of antipsychotic regimen (FGA, SGA and FGA + SGA) on the regression line among the different dosing methods.

Method	Line of best fit (r^2)		
	FGA	SGA	FGA + SGA
%BNF max versus CPZeq	0.74	0.61	0.32
%BNF max versus DDDs	0.70	0.28	0.20
CPZeq versus DDDs	0.90	0.38	0.54

be extrapolated to measure the antipsychotic dose when these drugs are used for other psychotic or mental disorders.

Early studies on antipsychotic drug utilization used CPZeq to assess the antipsychotic dose (Peralta et al., 1994; Warner et al., 1995). However, the CPZeq method has some drawbacks particularly the fact that the CPZeq values vary across literature and might not be accurate for SGA (Dewan and Koss, 1995). Furthermore, the values for CPZeq do not undergo annual revision after marketing the antipsychotic (Rey et al., 1989). The CPZeq is mainly based on dopamine-2 receptor activity, which is the major site of action of FGA. However, SGA act through a complex spectrum of receptor binding properties, which should be taken into account when comparing antipsychotic doses. This actually might partially explain the highest correlation between the three methods on patients receiving FGA while the correlation was weaker when the methods were applied to patients receiving SGA.

Although the BNF method is easy and available, it has some inherent problems. For example, the BNF is not adopted internationally and therefore different maximum recommended doses might be found in different formularies used by other countries. Despite this drawback, some investigators recommended the use of the BNF method instead of the CPZ method (Yorston, 2000).

A major advantage of the DDD method is that the DDD values are published by the WHO and readily and easily accessible for researchers. This enables investigators in different places to carry out comparisons with valid results.

Finally, the dose calculation methods investigated in this study are based on averages of doses recommended by manufacturers and approved by regulatory bodies or on expert-estimates of approximate clinically equivalent potency and not on research (Bezchlibnyk-Butler and Jeffries, 2007). However, a recent article has been published on international consensus on antipsychotic dosing based on opinions of a diverse group of international clinical and research experts (Gardner et al., 2010). In this study, participants ($N = 43$) from 18 countries provided dosing recommendations regarding treatment of psychotic disorders for 37 oral agents and 14 short-acting and 10 long-acting parenteral agents. With olanzapine 20 mg/day as reference, estimated clinical equivalency ratios of oral agents ranged from 0.025 for sulpiride to 10.0 for trifluperidol. Seventeen patient and treatment characteristics, including age, hepatic and renal function, illness stage and severity, sex, and diagnosis, were associated with dosing modifications (Gardner et al., 2010).

5. Conclusion

In conclusion, all three methods are reliable and coherent. The highest coherence was observed with CPZeq versus DDDs. In all three methods, coherence was strongest when dealing with FGA.

Disclosure statement

The authors state no conflict of interest.

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