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Brief report

Rates of study completion with single versus split daily dosing of antidepressants: a meta-analysis

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Abstract

Objective: To examine the tolerability of single versus multiple daily dosing (SDD vs. MDD) of antidepressant drugs in clinical practice. *Method:* Studies comparing single versus multiple daily dosing of antidepressants were reviewed. Since there were no numeric data available on the rates of adverse events for the SDD versus MDD arms, meta-analyses were carried out to compare rates of study completers (or rates of drop-outs) with single versus multiple daily dosing. *Results:* The review process identified 22 studies meeting our inclusion criteria. This meta-analysis found no difference in the rates of study completers with SDD or MDD regime of antidepressants. *Conclusion:* Our analysis on rates of completers (or rates of drop-outs) gives us an estimation of the overall acceptability of treatment and of course, but has limited utility when compared to the rates of adverse events. Yet, the present analyses suggest that adverse events which are significant enough to result in drop-outs, are not more frequent with SDD than MDD. MDD strategy of antidepressants does not seem to be more advantageous for the acceptability of treatment and obviously is disadvantageous for compliance. Thus, a simplified treatment regimen may be practical to increase treatment success rates in depression.

Keywords: Antidepressants; Single daily dosing; Acceptability; Compliance

1. Introduction

It is well known that treatment adherence of patients with depressive illness is far from being optimal, and non-compliance is one of the main reasons of the so-called 'treatment resistant' depression. In that sense, it may be advantageous to search for some fundamental strategies for improving efficacy of antidepressant treatment for this potentially deadly disease, such as a simplified treatment regimen. This strategy may improve compliance and in turn treatment success rates in depression.

In a recent meta-analysis, we have examined antidepressant drugs' treatment effects by stratifying medications according to the pharmacokinetic half-life of the drug, and showed no difference in the extent of clinical improvement between single daily dosing (SDD) and multiple daily dosing (MDD) for

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short, intermediate, and long half-life agents (Yildiz and Sachs, 2001). This suggests that sustained therapeutic serum levels are not necessary for achievement of therapeutic activity. In the present work, since there were no numeric data available for the rate of adverse events for the SDD versus MDD arms, we aimed to estimate tolerability of SDD versus MDD of antidepressant drugs in clinical practice by analyzing rates of completers over the studies we have identified (Yildiz and Sachs, 2001) in our first work.

2. Method

2.1. Meta-analysis procedure

We performed a meta-analysis as described in the paper by Ingelfinger et al. (1994), with weights being inversely proportional to the estimated variances of the differences. The rate difference of the ith study denoted by d_i, is the difference between the proportion of completers in the SDD (p_t) versus MDD (p_c) arms: $d_i = p_t - p_c$. The variance of the difference between two independent quantities is the sum of their variances. As the components of p_t and p_c are observed proportions, the variance of d is estimated as:

$$S_d^2 = \frac{vp_t(1-p_t)}{n_t} + \frac{vp_c(1-p_c)}{n_c}$$

where n_t and n_c are the sample sizes corresponding to SDD and MDD arms, respectively. The estimated standard deviation of d is S_d, and the 95% confidence limits for d are estimated as $d \pm 1.96 S_d$. Since the sets of studies we have differ in their sizes, we elect to use a weighted mean with the weights being inversely proportional to the variances of quantities being estimated. Since the weights must add to 1, we divide each reciprocal by the sum, S, of the reciprocals to get the weights. $S = 1/S_1^2 + 1/S_2^2 + 1/S_3^2 + \ldots + 1/S_k^2$. Then the weights, w_i for the individual study i are given by: $w_i = 1/S_i^2$. The weighted average is $d_w = w_1 d_1 + w_2 d_2 + w_3 d_3 + \ldots + w_k d_k$, and an estimate of its variance is: estimated variance of $d_w = 1/S$. A significant treatment effect ($P < 0.05$) is obtained if the 95% confidence interval for d_w does not include 0.

For the studies where probability of completers both in the SDD and MDD arms are 1, to obtain an estimate for the treatment (SDD) and control groups (MDD) we used the total number of completers divided by the total number of patients in the corresponding group over the set of studies we were analyzing. To be consistent with our first meta-analysis in this series, in this work we also applied the arbitrary drug/study separation based on $t_{1/2}$ of 12 and 24 h for short, intermediate, and long half-life groups, and ran meta-analyses both for each group and overall.

3. Results

3.1. SDD versus MDD of short half-life antidepressant agents ($t_{1/2} < 12$ h)

A total of 12 trials meeting our inclusion criteria compared SDD versus MDD dosing of antidepressant agents with elimination half-life of less than 12 h. None of these studies found a statistically significant difference in type or severity of adverse effects between the two dosing schedules. In this group all but one studies provided sufficient data for meta-analysis (Wheatley, 1980). Of the 11 studies analyzed in this group, one had a rate difference of 0 (Voris et al., 1998). For this study an estimate of variance is calculated and used in the analysis by pooling the data for the number of completers and total number of subjects for the SDD and MDD arms. This revealed a variance of 0.00364, and a weight of 0.1354 for that study. As the 95% CIs include 0, the individual rate differences were insignificant in each of the studies but one in this group (Ban et al., 1982). In that study rate difference favored SDD, by revealing a weighted mean difference of 0.0114. The sum, S, of the reciprocals of the estimated variances for this group is calculated to be 2027.9. The summary statistics for the 11 trials, with a weighted mean difference of 0.0203, estimates a better tolerability rate associated with SDD compared with MDD at slightly more than 2%. Because, the 95% CI (-0.0232; 0.0638) includes 0, the difference was statistically insignificant at the 5% level.

3.2. SDD versus MDD of intermediate half-life antidepressant agents (12 h<$t_{1/2}$<24 h)

For intermediate half-life antidepressant agents (with elimination half-life between 12 and 24 h), six studies met inclusion criteria. There were no significant differences between the two dosing schedules in type or severity of adverse effects. All six trials provided sufficient data on the rates of study completion for inclusion in the meta-analysis. As the 95% CIs include 0, the individual rate differences were insignificant in each of the studies but one in this group (Mendels and Schless, 1977). In that study rate difference favored SDD, by revealing a weighted mean difference of 0.0286. The sum, S of the reciprocals of the estimated variances for this group is calculated to be 668.3. The summary statistics for the six trials, with a weighted mean difference of 0.0467, estimates a better tolerability rate associated with SDD compared with MDD at less than 5%. Because the 95% CI (-0.0291; 0.1225) includes 0, this difference was statistically insignificant at the 5% level.

3.3. SDD versus MDD of long half-life antidepressant agents ($t_{1/2}$>24 h)

We identified four reports with five sets of data meeting our inclusion criteria for the antidepressant agents with long half-life (with elimination half-life more than 24 h). Similar to the results of studies in the other two groups, no study in this group reported a significant difference between SDD and MDD for the incidence and severity of adverse events. A meta-

Table 1
Weighted mean of the rate differences with weights inversely proportional to the estimated variances of the differences for all the antidepressant agents reviewed

Source[a]	Sample size, SDD/MDD	No. of patients completing study, SDD/MDD	Variance, S_i^2	1/Variance, $1/S_i^2$	Weights, $w_i=1/S_i^2 S$	Rate difference, d_i	Weight × difference $w_i d_i$
De Maio et al., 1981	15/15	15/13	0.007704	129.8	0.0257	0.1333	0.0034
Amsterdam et al., 1998	25/23	21/21	0.008826	113.3	0.0224	−0.0730	−0.0016
Mungavin and Ankier, 1983	98/97	73/67	0.004141	241.5	0.0478	0.0542	0.0026
Davey, 1988	95/87	77/70	0.003414	292.9	0.0580	0.0101	0.0006
Brooks et al., 1984	29/27	17/20	0.015477	64.6	0.0128	−0.1545	−0.0020
Wheatley, 1984	79/67	60/50	0.005138	194.6	0.0385	0.0132	0.0005
Reimherr et al., 1998	121/120	66/67	0.004104	243.7	0.0483	−0.0129	−0.0006
Voris et al., 1998	3/3	3/3	0.000440	2272.7	0.4500	0.0144	0.0065
Ban et al., 1982	17/18	17/14	0.009602	104.1	0.0206	0.2222	0.0046
Newburn et al., 1995	94/95	72/73	0.003780	264.6	0.0524	−0.0025	−0.0001
Watson and Tiplady, 1981	15 QD nocte/ 13 BID	14/12	0.009610	104.1	0.0206	0.0103	0.0002
Mendels and Schless, 1977	22/22	20/14	0.014275	70.1	0.0139	0.2727	0.0038
Mendels and Schless, 1975	21/19	20/16	0.009158	109.2	0.0216	0.1103	0.0024
Weise et al., 1980	62/62	40/45	0.006902	144.9	0.0287	−0.0807	−0.0023
James and Dean, 1980	42/38	37/34	0.004975	201.0	0.0398	−0.0138	−0.0005
Snowdon, 1976	25/25	21/20	0.011776	84.9	0.0168	0.0400	0.0007
Siddiqui et al., 1985	21 QD, nocte	17/13	0.017169	58.2	0.0115	0.1905	0.0022
Khorana, 1981	20/20	18/18	0.009000	111.1	0.0220	0.0000	0.0000
Frank, 1977	20/17	14/14	0.019049	52.5	0.0104	−0.1235	−0.0013
Frank, 1977	17/16	10/11	0.027676	36.1	0.0071	−0.0993	−0.0007
Schubert and Miller, 1978	14/14	6/5	0.033892	29.5	0.0058	0.0714	0.0004
Montgomery et al., 1978	29/28	26/24	0.007571	132.1	0.0262	0.0394	0.0010
				$S=5055.5$	1.0009 ≈ 1		$d_w=0.0198$

$1/S=0.000198$; confidence interval for d_w: -0.0078; 0.0474.

[a] For the antidepressant drugs used in the individual studies please refer to Yildiz and Sachs, 2001.

analysis was carried out including the five sets of data in this group. Since all the 95% CIs include 0, the individual rate differences were insignificant in each of the studies in this group. The sum, S of the reciprocals of the estimated variances for this group is calculated to be 361.3. The summary statistics for the five trials, with a weighted mean difference of -0.0076, estimates a better tolerability rate associated with MDD compared with SDD at slightly less than 1%. Because the 95% CI (-0.1107; 0.0955) includes 0, this difference was statistically insignificant at the 5% level.

Finally, to address the tolerability of SDD versus MDD overall, a meta-analysis was performed based on all 22 studies. To deal with the rate difference of 0 in the study of Voris et al. (1998), an estimate of variance is calculated and used in the analysis by pooling the data over the 22 studies. This revealed a variance of 0.00044, and a weight of 0.45 for that study. The rate differences, estimate of variances, and weights of individual studies for this analysis are documented in Table 1. The sum, S, of the reciprocals of the estimated variances for this analysis is calculated to be 5055.5. A weighted mean difference of 0.0198 estimated a better tolerability rate associated with SDD compared with MDD at slightly less than 2%. However, the 95% CIs (-0.0078; 0.0474) revealed insignificance for this difference at the 5% level (Table 1).

4. Discussion

Overall, this meta-analysis found no difference in the rates of completers with SDD or MDD regime of antidepressants. It has long been known that a complex therapeutic regimen provokes non-compliance. In a systematic review of 57 articles, Greenberg (1984) found a 73% compliance rate for QD (once a day) dosing, 70% for BID (twice a day), 52% for TID (three times a day), and 42% for QID (four times a day). In a study made in epileptic patients compliance rate was 87% in QD dosing while it was only 39% in QID dosing (Cramer et al., 1989). In the psychiatric field, Ayd (1972) reported that 70% of outpatients failed to take 25–50% of their prescribed dose while on QID regimen, and this figure dropped to only 7% non-compliance on a once-daily dose regimen.

In addition, patients with depressive illness are especially prone to non-compliance for several reasons. First, unipolar depression is a chronic, recurrent condition that needs long-term treatment with the acute antidepressant dose. For many depressive patients, lifetime pharmacologic maintenance may be indicated, and it has been shown that depressive patients' compliance tends to decline with time (at 3, 6, 9, and 12 weeks of treatment: 68, 63, 50 and 40%, respectively; Myers and Branthwaite, 1992). Second, while some aspects of depression such as cognitive impairment, helplessness, poor motivation and withdrawal may lead to forgetfulness and passive non-compliance, some other aspects like exaggerated guilt may make depressive patients feel that they do not deserve treatment, and this in turn inevitably lessens their motivation for treatment (Demyttenaere, 1997). Third, diseases where the association between non-compliance and recurrence is not very clear "as in the case with depressive illness" are more vulnerable to culminate with poor compliance (Demyttenaere, 1997). These points, together with a 30% reported rate of treatment resistant depression, which is strongly associated with non-compliance (Souery and Mendlewicz, 1998), underline the potential impact of a simplified treatment regimen for the management of depressive illness.

Our analysis on rates of completers (or rates of drop-outs) gives us an estimation of the overall acceptability of treatment and of course, but has limited utility when compared to the rates of adverse events. Nonetheless, in clinical trials there are several reasons for droping out, which are, for the most part, adverse events, inefficacy, and treatment complexity. Among these, we have demonstrated that neither inefficacy nor treatment complexity is in question for the SDD strategy. However, with regard to adverse events, since most of the studies included have not given numeric data on the adverse events rates but simply stated insignificance between the SDD versus MDD arms, reported data were insufficient for making a direct systematic analysis on this. Yet, the present analyses on the rates of completers suggest that adverse events, which are significant enough to bring about drop-outs, are not more frequent with SDD than MDD. Although individual studies are questionable in power, no study included in our analyses has found significant differences in the

incidence or extent of adverse events between SDD and MDD.

In conclusion, this analysis on the rates of completers and our prior meta-analysis on efficacy may validate implementation of SDD strategy of antidepressants in clinical practice. Future clinical trials will clarify if there is a particular group of depressive patients for whom SDD or MDD would be more beneficial, and also if the specific data on the rates of adverse events with SDD and MDD will prove to be different than the tolerability estimations based on the rates of completers of the present report.

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