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Research report

Administration of antidepressants Single versus split dosing: a meta-analysis

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Abstract

Objective: To evaluate the literature comparing antidepressant effects of multiple daily dosing versus single daily dosing of antidepressants. *Method:* Studies comparing efficacy of single versus multiple daily dosing of antidepressants were reviewed. Data from the clinical trials meeting our inclusion criteria was subgrouped according to the half-life of the antidepressant drug studied. Meta-analyses were carried out to compare antidepressant efficacy of single versus multiple daily dosing overall and separately for the short, intermediate, and long half life antidepressant agent subgroups. *Results:* The review process identified 22 studies comparing the therapeutic effect of antidepressants according to their dosing schedules. Although most studies used antidepressant medications with short half-lives, none found a significant difference in therapeutic efficacy. Furthermore, the improvement rates in depression scores in between the two groups were almost identical (SDD versus MDD). *Conclusion:* This meta-analytic approach found no advantage for multiple daily dosing and suggests that sustained therapeutic serum levels are not necessary for achievement of therapeutic activity. Antidepressant benefit may simply require a limited duration of exposure above the threshold serum level. Administration of antidepressants in single daily doses appears sufficient to perturb the physiological pathways associated with depression sufficiently to achieve an adaptive therapeutic response. Moreover, a single daily dosing regimen offers the potential advantages of simplicity, increased compliance, and reduced adverse effects, which in turn would increase the overall success rate in treatment of depression.

Keywords: Antidepressants; Meta-analysis; Dosing schedule; Adaptation; Compliance

1. Introduction

Multiple daily dosing for antidepressant drugs is a problematic strategy, without evidence of necessity. Splitting the dose may improve the tolerability of medication, which would otherwise be unacceptable. This seemingly reasonable strategy is, however, often counterproductive. Multiple dosing reduces compliance and can decrease the acceptability of some medications. This is particularly true when intolerable side effects are related to peak serum

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Table 1
Elimination half-lives of the antidepressant agents reviewed

Drug	Mean elimination half-life after single oral dose (h)
Imipramine	28.0
Desipramine	21.0
Clomipramine	24.7
Amitriptiline	21.0
Doxepine	17.0
Mianserin	6.0–40.0
Nomifensin	1.5–2.0
Fluvoxamine	15.0
Venlafaxine	3.6
Nefazodone	3.0
Trazodone	7.0
Amoxapine	8.0
Moclobemide	1.0–2.0
Zimelidine	5.1
Bupropion	9.8

levels. Instead of a single peak occurring while the patient is asleep, multiple peaks must be endured during working hours.

Antidepressants are often dosed on a schedule, which assumes that antidepressant benefit requires sustained serum levels above a therapeutic level. This assumption suggests single daily dosing is appropriate only for long half-life drugs. To examine the issue of multiple versus single daily dosing we identified and analyzed the results of studies with long, medium, and short half-life antidepressants (see Table 1 for elimination half-lives of the antidepressants reviewed) addressing these questions:

1. Does once daily dosing of antidepressants differ from multiple daily dosing in their efficacy for treatment of depression?
2. Does antidepressant activity change according to the pharmacokinetic half-life of the drug when it is given as a single daily dose? Or, are antidepressant drugs with short elimination half-lives ineffective when administered as a single daily dose?

2. Method

2.1. Selection of studies

A computer search was carried out to identify studies comparing single versus multiple daily doses, using ‘antidepressants’, ‘single daily dosing versus’, ‘multiple daily dosing’, and ‘antidepressant efficacy’ as key words. Efficacy studies comparing dosing schedules of antidepressants were included in the data analysis if:

1. assignment to treatment was randomized,
2. one of the study arms utilized once daily dosing strategy,
3. the multiple and single daily dosing regime used the same antidepressant agent,
4. the dose in the once daily dosing arm did not exceed the total daily dose in the multiple daily dosing arm.

2.2. Meta-analysis procedure

A meta-analysis provides a systematic and quantitative approach to the summary of results from randomized studies and can be performed in a variety of ways corresponding to different selection of weights for the individual studies. We performed a meta-analysis, as described in Whitehead and Whitehead (1991), with weights chosen to be the inverse variance of treatment effects in each study and only included studies with sufficient data. The treatment effect of the ith study, denoted by θ_i, is the difference between the change from the baseline between the SDD and MDD arms:

$$\theta_i = \bar{B}_S - \bar{F}_S - (\bar{B}_M - \bar{F}_M)$$

where, $\bar{B}_S$ and $\bar{F}_S$ are the means of the HAM-D scores in the SDD arm at the baseline and study end point, respectively, and $\bar{B}_M$ and $\bar{F}_M$ are the means of the HAM-D scores in the MDD arm at the baseline and study end point, respectively, for the individual study, i.

The weights, ω_i, are the inverse variance of the treatment effect for the individual study, i, and are given by:

$$\omega_i^{-1} = \frac{2(1-\rho_M)V_M}{N_M} + \frac{2(1-\rho_S)V_S}{N_S}$$

where V_M is the variance of the improvement in the HAM-D score, ρ_M is the correlation between the baseline and final HAM-D scores, and N_M is the

number of subjects who completed the study in the MDD arm. Similarly, V_S is the variance of the improvement in the HAM-D score, ρ_S is the correlation between the baseline and final HAM-D scores, and N_S is the number of subjects who completed the study in the SDD arm for the individual study, *i*.

Unfortunately, previous publications did not report correlation between the baseline and the follow-up scores (ρ_S and ρ_M) which are necessary to calculate the weights, ω_i. In fact, it is unclear whether these publications accounted for this correlation in their statistical tests. Also, previous studies may have used different test statistics, which did not require correlation such as, $\theta_i = \bar{F}_S - \bar{F}_M$.

For this reason we assumed $V(B_S) = V(F_S) = V_S$ [i.e., $V(B_S)$ is the variance of the baseline HAM-D score and $V(F_S)$ is the variance of the final HAM-D score of the SDD arm], similarly $V(B_M) = V(F_M) = V_M$ [i.e., $V(B_M)$ is the variance of the baseline HAM-D score and $V(F_M)$ is the variance of the final HAM-D score of the MDD arm], and $\rho_M = \rho_S = \rho$ and computed test statistics, *u*, for $\rho = 0$, 0.5, and 0.9. The value $\rho = 0.9$ is the worst-case scenario (high correlation). If *u* is insignificant for $\rho = 0.9$, then *u* is not significant for $\rho = 0.5$ and $\rho = 0$ (independence).

Previous publications give us $V(B_M)$, $V(F_M)$, $V(B_S)$, and $V(F_S)$; and based on the first assumption we calculated V_M and V_S.

The statistics for testing the null hypothesis of no treatment effect, i.e., $H_0 = \theta_{SDD} = \theta_{MDD}$, for the $i = 1, \ldots\ldots\ldots, n$ (total number of studies) is

$$u = \frac{(\sum \theta_I \omega_i)^2}{\sum \omega_i}$$

where *u* follows a chi-square distribution with one degree of freedom. A significant treatment effect (*P*-value of <0.05) is obtained if $u > 3.84$.

We applied this meta-analysis procedure to 17 studies, which provided sufficient data (see Tables 2–4. Among the 17 studies, seven did not report standard deviations (S.D.) of the means. For these studies an estimate of the S.D. based on an interpolation of reported S.D.s is calculated and used in the analysis. First we performed a meta-analysis for all the 17 studies, and then we grouped the studies according to the half-life of the study drug and a separate meta-analyse for each group.

3. Results

The search returned 1616 reports of which 32 involved a comparison of single versus multiple daily dosing of antidepressants and 22 met our inclusion criteria (Tables 2–4).

To address the overall issue of SDD versus MDD, a meta-analysis was performed based on all 17 reports, which provided sufficient data for analysis. The findings from the other five studies, which did not provide sufficient data for the meta-analysis procedure, are also summarized in Tables 2–4. Estimate of variances based on the entire data is calculated to be $V_S = 30.2$ and $V_M = 49.8$. The treatment effects of individual studies are documented in Tables 2–4. Even with the worst-case scenario, the test statistic ($u = 0.299$, $P > 0.5$) is well below the critical value (3.84) for significance. This overall analysis revealed no significant difference ($\rho = 0.9$) in the effectiveness of SDD and MDD of antidepressants in general. (Fig. 1)

The same procedure was repeated for the analysis of the studies subgrouped on the basis elimination half-life (see Table 1).

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

Twelve trials meeting our inclusion criteria compared SDD vs. MDD dosing of antidepressant agents with elimination half-lives of less than 12 h (Table 2). None of these studies found a statistically significant difference in the onset or extent of this clinical improvement and each report considered both dosage regimens efficacious in relieving depression. There were no significant differences between the two dosing schedules in type or severity of adverse effects.

In this group ten studies provided sufficient data for meta-analysis. The treatment effects and the weights of the individual studies with short half-life antidepressants are presented in Table 2. The estimate of variances for this group is calculated to be $V_S = 25.7$ and $V_M = 21.7$ and test statistic $u = 1.188$ (critical value 3.84). The difference between the SDD and MDD arms for the antidepressant effect not significant ($P > 0.2$). The average improvement observed with SDD and MDD of antidepressants with

Table 2
Summary of data for the antidepressant agents with short half-life $t_{1/2} < 12$ h

Study	Design	Drug	Dose (mg/day) SDD/MDD	Sample size SDD/MDD	Treatment effect (θ)	Weight (ω) of treatment effect[a]	Compliance (%) SDD/MDD	Mean baseline rating SDD/MDD	%Δ at the end-point SDD/MDD
De Maio et al., 1981	Random	Nomifensine	100–200/ 100–200	15/15	−2.8	8.285	100/86	HAM-D 27.13/29.31 Zung SRDS 50.57/49.92	HAM-D 46.3/49.6 Zung SRDS 33.5/23.8
Amsterdam et al., 1998	Double-blind Random	Venlafaxine	150–225/ 150–225	25/23	−0.2	2	84/91	HAM-D 24.5/22.6 MADRS 27.4/25.5	HAM-D 56.3/61.9 MADRS 61.7/67.4
Mungavin and Ankier, 1983	Random	Trazodone	200/200	98/97	−0.5	10.395	74/69	HAM-D 24.8/24.8	HAM-D 64.1/66.1
Davey, 1988	Double-blind Random	Trazodone	150/150	95/87	−1.4	7.2098	81/80	HAM-D 23.0/23.2	HAM-D 57.8/63.4
Brooks et al., 1984	Double-blind Random	Trazodone	200–400/ 200–400	29/27	3.5	1.9253	59/74	HAM-D 26.5/22[b] MADRS 28.5/24	HAM-D 54.7/50 MADRS 49/29
Wheatley, 1980	Random	Trazodone	50–200/ 50–200/ 50–200	34 QD/ 33 BID/ 20 TID	–	–	Not stated	No significant difference between groups, not stated in detail	
Wheatley, 1984	Double-blind Random	Trazodone	100–150/ 100–150	79/67	3.9	5.7971	76/75	HAM-D 26.3/24.5[b]	HAM-D 72/61
Reimherr et al., 1998	Double-blind Random	Bupropion	150/300	121/120	–	–	54.5/55.8	No significant difference, between groups data unavailable	
Voris et al., 1998	Random	Nefazodone	400–500/ 400–500	3/3	−0.9	0.1265	100/100	HRS (self rep. version) 37.9/38.5	HRS 24.5/26.5
Ban et al., 1982	Double-blind Random	Amoxapine	150–400/ 150–400	17/18	−1.7	1.6329	100/78	HAM-D 28.7/30.0	HAM-D 72/74
Newburn et al., 1995	Double-blind Random	Moclobemid	450–600/ 450–600	94/95	0.36	9.7943	77/77	HAM-D 23.4/23.2	HAM-D 73.8/72.9
Watson and Tiplady, 1981	Double-blind Random	Zimelidine	200/200	15 QD noc/13 BID	−3.5	1.3287	93 QD noct /92 BID	HAM-D 15.2/17.7	HAM-D 11/29

[a] Weights, ω_i, are reported based on interpolations within the group.
[b] Numeric data is estimated from the graphic presentation.

Table 3
Summary of the data for antidepressant agents with intermediate half-life, $12 < t_{1/2} < 24$ h

Study	Design	Drug	Dose (mg/day) SDD/MDD	Sample size SDD/MDD	Treatment effect (θ)	Weight (ω) of treatment effect[a]	Compliance (%) SDD/MDD	Mean baseline rating SDD/MDD	%Δ at the end-point SDD/MDD
Mendels and Schless, 1977	Double-blind Random	Desipramine	150/150	22/22	2.7	3.1576	91/64	HAM-D 35.5/34.2	HAM-D 55/49
Mendels and Schless, 1975	Double-blind Random	Doxepin	100/100	21/19	4.34	3.3356	95/80	HAM-D 37.72/36.50	HAM-D 62/52
Weise et al., 1980	Double-blind Random	Amitriptyline	150/150	62/62	–	–	65/73	Beck Dep. Inv.[b] 17.62	Beck Dep Inv 61.3/43.4[c]
James and Dean, 1980	Random	Amitriptyline–chlordiazopoxide (15 mg) combination	37.5–75/ 37.5–75	42/38	–	–	89[b]	Leeds DS 11.9/11[c]	Leeds DS 57/48[c]
Snowdon, 1976	Double-blind Random	Amitriptyline	150/150	25/25	–	–	84/80	HAM-D (stated as being equally effective)	
Siddiqui et al., 1985	Double-blind Random	Fluvoxamine	100/ 100	21 QD, nocte 21 TID	0.6	2.7847	81/60	HAM-D 21.5 QDN/ 21.8 TID	HAM-D 57.8 QDN/ 53.3 TID

[a] Weights, ω_i, calculated based on reported and interpolated S.D.s and $\rho = 0.9$ within the group. Weights for $\rho = 0$ and $\rho = 0.5$ were proportional to weights for $\rho = 0.9$.
[b] For whole sample.
[c] Numeric data is estimated from the graphic presentation.

Table 4
Summary of data for the antidepressant agents with long half-life, $t_{1/2} > 24$ h

Study	Design	Drug	Dose (mg/day) SDD/MDD	Sample size SDD/MDD	Treatment effect (θ)	Weight (ω) of treatment effect[a]	Compliance (%) SDD/MDD	Mean baseline rating SDD/MDD	%Δ at the end-point SDD/MDD
Khorana, 1981	Double-blind Random	Imipramine	150/150	20/20	0.6	28.0899	90/90	HAM-D 31.1/31.8	HAM-D 93/89
Frank, 1977	Random	Clomipramine	30/30	20/17	0.2	1.1041	70/82	HAM-D 24.7/23.9	HAM-D 65/67
			75/75	17/16	−5.6	0.84	59/69	HAM-D 24.4/23.1	HAM-D 50/77
Schubert and Miller, 1978	Double-blind Random	Clomipramine	150/150	14/14	–	–	43/36	HAM-D[b] 22.3	HAM-D[b] 60.4
Montgomery et al., 1978	Double-blind Random	Mianserin	60/60	29/28	1.2	0.996	90/86	HAM-D 25.5/23.7	HAM-D 52/51

[a] Weights, ω_i, calculated based on reported and interpolated S.D.s and $\rho = 0.9$ within the group. Weights for $\rho = 0$ and $\rho = 0.5$ were proportional to weights for $\rho = 0.9$.
[b] For whole sample.

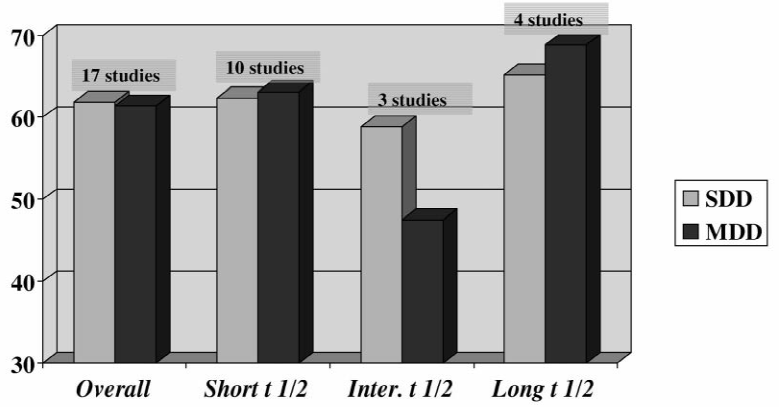

Fig. 1. The weighted average mean of the percentage of improvements in the HAM-D scores with different dosing schedules of short, intermediate, and long half-life antidepressants, and the number of studies included in each meta-analysis.

short half-life was nearly the same (61.04 and 61.98%, respectively). (Fig. 1)

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

For intermediate half-life antidepressant agents, six studies meet the inclusion criteria (Table 3). In each of these trials, both SDD and MDD strategies showed a significant improvement from baseline to final evaluation on the total score of the depression scale administered. None of the studies showed a significant difference in antidepressant efficacy between the groups. There were no significant differences between the two dosing schedules in type or severity of adverse effects. Of these six trials, three provided sufficient data for inclusion in the meta-analysis (see Table 3). Estimate of variances for this group is calculated to be $V_S = 18.1$ and $V_M = 9.5$. Using the worst-case scenario ($\rho = 0.9$), the test statistics $u = 65.613$ (exceeds critical value 3.84) indicated a significant difference ($P < 0.0001$) among the treatment effects of the SDD and MDD strategies in favor of the SDD strategy. However, the worse case scenario was adopted to avoid falsely concluding no benefit of MDD and the result of the analysis here favors SDD. Therefore, the conservative approach for this situation is to consider more likely possible scenarios such as modest correlation ($\rho = 0.5$) and no correlation ($\rho = 0$). For both these scenarios the results remained statistically significant ($\rho = 0.5$, $u = 13.124$, $P = 0.0003$ and $\rho = 0.0$, $u = 6.617$, $P = 0.01$). Interestingly, all three studies included in the meta-analysis of this group found non-significant results and the first two reported a trend in the favor of SDD. However, they were looking at different measures of comparison than the change from the baseline as considered in this analysis as a treatment effect. This accounts for the missing reports of correlation. Our own analysis of each study individually using the weights and the treatment effects reported would have found significance for these first two studies but not the last (Table 3).

The average improvement observed with the SDD of antidepressants with intermediate half-lives was superior to the MDD (58.36 and 51.37%, respectively) (Fig. 1).

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

We identified five dosing schedule comparison trials meeting our inclusion criteria for the antidepressant agents with long half-lives (Table 4). Similar to the results of the studies in the other two groups, no study in this group found significant differences between SDD and MDD for antidepressant efficacy or the incidence and the severity of side effects. A meta-analysis was carried out including the four studies that provided sufficient data for inclusion (see Table 4). The estimate of variances for

this group was calculated to be $V_S = 20.8$ and $V_M = 42.6$. Using the worst-case scenario ($\rho = 0.9$), the test statistics $u = 5.93$ (exceeds critical value 3.84) indicated a significant difference ($P = 0.01$) among the treatment effects of the SDD and MDD strategies in favor of the SDD strategy. However, since the worse case scenario was adopted to avoid falsely concluding no benefit of MDD and as the result of the analysis here favors SDD, we repeated the same analysis with more likely possible scenarios such as modest correlation ($\rho = 0.5$) and no correlation ($\rho = 0$). For these more likely scenarios the results were not statistically significant ($\rho = 0.5$, $u = 2.166$, $P > 0.1$ and $\rho = 0.0$ $u = 0.594$, $P > 0.4$). The average improvement observed with SDD and MDD of antidepressants with long half-lives was nearly the same (89.52 and 86.67%, respectively) (Fig. 1).

4. Discussion

Overall, this meta-analysis found no difference in the efficacy of antidepressants administered on a SDD or a MDD regime. Separate meta-analyses comparing SDD and MDD strategy for drugs grouped by half-life found no advantage of MDD. For those with an intermediate half-life, SDD was significantly more effective than MDD. Given the limited number of studies in the intermediate half-life group and the assumptions of the meta-analysis procedure, however, this data does not conclusively demonstrate the superiority of SDD even for intermediate half-life antidepressants. Rather, the data suggests the efficacy of SDD is no less than, but could be superior to, the efficacy of MDD.

While meta-analysis is subject to bias arising from a tendency for published reports to contain only significant results, our search to identify efficacy comparison trials of SDD and MDD antidepressants returned 22 studies each reporting non-significant results. Therefore, we assume publication bias did not influence this meta-analysis.

As reviewed by Souery and Mendlewicz (1998) up to 30% depressed patients fail to respond to treatment with standard antidepressive pharmacotherapy, and among treatment resistant cases as many as 20% are non-compliant. The unnecessary complexity of a MDD therapeutic regimen can contribute to non-compliance and may account for a substantial proportion of treatment failure. Improved compliance with single daily dosing of medications (Ayd, 1972, 1974; Greenberg, 1984; Cramer et al., 1989; Eisen et al., 1990) may improve the treatment success rate.

Although adverse effect data was not sufficient for meta-analysis, and it is unlikely that any individual study was powered to detect differences in adverse effects, no study found significant differences in adverse effect rates between SDD and MDD.

Findings from molecular psychopharmacology are compatible with the results of this meta-analysis. The brain's response to chronic administration of antidepressant drugs has been associated with down regulation of postsynaptic β-adrenergic receptors (Sulser et al., 1978; Schultz et al., 1981; Heninger and Charney, 1987; Sulser, 1989), desensitization of 5-HT 1_A autoreceptors present on serotonergic neuronal cell bodies (Heninger and Charney, 1987; Blier and De Montigny, 1994; Stahl, 1998), and regulation of tyrosine hydroxylase activity in the dopaminergic brain regions (Rosin et al., 1995). Adaptation (see review by Hyman and Nestler, 1996) may not require constant exposure above a threshold to achieve therapeutic results. Our meta-analysis of the data suggests that SDD is adequate to achieve an adaptive therapeutic response.

In conclusion, our analysis indicates that the needs of individual patients rather than half-life should determine dosing schedule when prescribing antidepressants.

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