LETTER TO THE EDITOR

Suicidal Risks in Reports of Long-Term Controlled Trials of Antidepressants for Major Depressive Disorder II

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Professor Roland Dardennes and colleagues (2016) noted differences with respect to several numerical values included in our recent letter concerning suicidal risks in reports of randomized, long-term, placebo-controlled trials of antidepressants for major depressive disorder (Baldessarini et al. 2016), based on a comprehensive review and meta-analysis of such studies (Sim et al. 2015). We appreciate their efforts to improve accuracy in reporting findings from this complex body of studies. The noted numerical differences did not alter the conclusion that rates of suicidal behavior in such trials were surprisingly high. Nevertheless, their observations led us to re-review the reports cited in detail, with independent data-extraction by 2 senior investigators (R.J.B. and K.S.) working to consensus. We encountered findings that required some judgment to represent them fairly and found 5 additional reports to include. This process led to a revised tabulation of our findings from 17 long-term, placebo-controlled antidepressant trials (Table 1).

Revised overall incidence rates (% of persons/y) with all treatments were: suicidal ideation, 2.08 (CI: 1.72–2.48); suicide attempts, 0.652 (0.459–0.897); suicides, 0.264 (0.148–0.435) (Table 1). Of note, these overall rates of suicidal subjects were significantly greater with antidepressants vs placebos (Table 1). This separation also obtained for attempts and suicides combined (0.740 vs 0.176; $P < .0001$) (Table 1). The observed overall suicide rate (264/y/100 000) in these trials for initially acutely depressed subjects is 18–26-times higher than international general population rates of 10–15/year/100 000, and about 5.3 times that in clinical samples of patients diagnosed with major depressive disorder in various states of illness and recovery (50/year/100 000; Tondo et al., 2007). If exposure times are adjusted for studies with high dropout of one-half or more of the participants to one-half

of the nominal or maximum times, then the observed overall rate of suicides is even higher (360/y/100 000), approximately 29 times above general population rates and 7.2 times higher than in clinical samples of patients with major depressive disorder. Also of note, the ratio of attempts/suicides of 2.47 (652/264) is far lower than in the general population (approximately 30) and lower than in clinic samples of major depression patients (approximately 5), suggesting greater lethality of attempts in trials (Tondo et al., 2007).

Such observed rates of suicidal events in long-term controlled trials of antidepressants may be misleading but support the hypothesis that suicidal risks in controlled treatment trials for depression are substantial and require further research. Most long-term antidepressant trials do not even comment on suicidal events, and those that do appear to consider them as passively acquired, incidental examples of adverse events (Sim et al., 2015; Baldessarini et al., 2016). In addition, the few reports with some data concerning suicidal behavior may involve unrepresentative, selective reporting of suicidal acts (attempts and suicides). Moreover, suicidal *ideation* almost certainly is unevenly and probably severely underreported, given the wide range of rates, and there is even lack of noting ideation despite occurrence of attempts or suicides (Table 1). The greater observed risks associated with antidepressant treatment are particularly surprising in view of the greater risk of depressive relapses of recurrences in placebo arms of the reported trials and the adverse effects of antidepressant discontinuation (Baldessarini et al., 2010, 2015). The apparently greater suicidal risks with antidepressant treatment may reflect greater exposure of antidepressant- than placebo-treated subjects: 30% greater numbers (3086/2372) and 35% longer observation times (1.19/0.88

Table 1. Suicidal Events in Long-term, Placebo-Controlled Treatment Trials for Major Depressive Disorder

Study	Treatment	Exposure (y)		Dropout (%)	Subjects (n)		Ages (y)	Suicidal Cases		Incidence (cases/100 person-years)	
		Drug	Placebo		Drug	Placebo		Drug	Placebo	Drug	Placebo
Rouillon et al. 1989	Maprotiline	1.17	1.00	35.8	767	374	46.0 (45.3–46.7)	0/9/5	0/0/1	14/897 (1.56)	1/374.0 (0.27)
Doogan and Caillard 1992	Sertraline	1.02	0.85	70.0	185	110	51.0 (19–78)[a]	0/2/1	0/1/0	3/189 (1.59)	1/93.5 (1.07)
Montgomery and Dunbar 1993	Paroxetine	1.15	1.00	44.8	68	67	47.1 (45.6–48.6)	0/0/1	0/0/0	1/78.2 (1.28)	0/67.0 (0.00)
Lauritzen et al. 1996	Paroxetine[b]	0.58	0.50	31.4	18	17	68.5 (66.0–71.0)	0/0/1	0/0/1	1/10.4 (9.62)	1/8.50 (11.8)
Versiani et al. 1999	Reboxetine	0.96	0.88	20.9	145	141	42.9 (41.5–44.3)	0/0/1	0/0/0	1/139 (0.72)	0/124 (0.00)
Rouillon et al. 2000	Milnacipran	1.50	1.00	58.0	104	110	46.6 (45.6–47.5)	0/8/2	0/5/1	10/156 (6.41)	6/110 (5.45)
Schmidt et al. 2000	Fluoxetine	0.73	0.48	46.2	379	122	41.5 (40.5–42.5)	1/0/0	1/0/0	1/277 (0.36)	1/58.6 (1.71)
Thase et al. 2001	Mirtazapine	0.96	0.77	65.6	76	80	39.8 (38.8–40.8)	0/2/0	0/0/0	2/73.0 (2.74)	0/61.6 (0.00)
Kornstein et al. 2006	Escitalopram	1.46	1.00	79.1	73	66	41.4 (40.2–42.6)	0/0/0	0/1/0	0/107 (0.00)	1/66.0 (1.52)
Perahia et al. 2006	Duloxetine	0.73	0.50	87.1	136	142	44.0 (43.1–44.9)	0/3/1	0/0/0	4/99.3 (4.03)	0/71.0 (0.00)
Keller et al. 2007[c]	Venlafaxine	2.60	2.00	40.5	43	86	44.3 (44.1–44.5)	0/0/0	1/0/0	0/112 (0.00)	1/172 (0.58)
Kocsis et al. 2007[c]	Venlafaxine	1.69	1.00	67.3	129	129	42.3 (42.2–42.4)	1/0/0	1/0/0	1/218 (0.46)	1/129 (0.78)
Kelin et al. 2010	Duloxetine	1.65	1.00	47.6	64	60	46.3 (45.0–47.6)	0/0/0	0/0/0	0/106 (0.00)	0/60.0 (0.00)
Liebowitz et al. 2010	Quetiapine	1.40	1.00	99.2	387	384	43.5 (42.8–44.1)	9/0/0	1/0/0	9/542 (1.66)	1/384 (0.26)
Yildiz et al. 2010	Sertraline[b]	0.35	0.35	65.2	36	16	45.4 (25–64)a	4/0/0	0/0/0	4/12.6 (31.8)	0/5.60 (0.00)
Boulenger et al. 2012	Vortioxetine	1.46	1.23	64.2	204	192	44.7 (43.9–45.5)	1/1/0	0/0/0	2/298 (0.67)	0/236 (0.00)
Rosenthal et al. 2013	Desvenlafaxine	0.88	0.38	55.8	272	276	45.9 (44.8–47.0)	76/5/0	22/0/0	81/239 (33.9)	22/105 (21.0)
Totals/means	17 trials	1.19	0.88	57.6	3086	2372	46.0	92/30/12	26/7/3	134/3552 (3.77)[d]	36/2126 (1.69)[d]
(95% CI)		(0.92–1.47)	(0.68–1.08)	(47.1–68.1)			(42.7–49.2)	(134)	(36)	(3.07–4.31)	(1.21–2.38)

The 17 trials included 5458 depressed subjects.

[a] Range.

[b] Also given ECT in both trial-arms.

[c] Early and late phases of the same trial.

[d] Based on sum of individual patient-year exposures; pooled rates differ highly significantly ($r^2 = 17.2$, $P < .0001$), but means of individual studies: drug = 5.69 (CI: 0.27–11.1), placebo = 2.61 (0.00–5.49) cases/100 person-years do not ($t = 1.06$, $P = .30$). Overall rates (drug+placebo arms): ideation = 118/5678 = 2.08 (CI: 1.72–2.48); attempts: 37/5678 = 0.652 (0.459–0.897); suicides: 15/5678 = 0.264 (0.148–0.435) cases/100 person-years (or 264/y/100000 [148–435]). Rates for suicides+attempts differ significantly between antidepressant- (0.740 [0.534–0.999] %/y) and placebo-treated subjects (0.176 [0.084–0.324] %/y, $r^2 = 19.8$, $P < .0001$) Mean exposure adjusted by one-half for trials with dropout rates of ≥50% = 0.857 (0.668–1.05) years for antidepressants and 0.641 (0.415–0.867) for placebo, leading to an adjusted rate of suicides of 15/4165 = 0.360 (0.207–0.593) suicides/person-year (360/y/100,000 [CI: 207–593]). Mean ages are similar across trials and similar in treatment-arms randomized to drug vs placebo.

years), which in most trials included several months of open-label and stabilization phases involving antidepressant but not placebo treatment. In addition, dropout and relapse rates were consistently greater in placebo arms of trials: among 5 reports with flow charts to account for the dispositions of all subjects and treatments (Kornstein et al., 2006; Parahia et al., 2006; Keller et al., 2007; Kelin et al., 2010; Liebowitz et al., 2010; Rosenthal et al., 2013), rates of early loss averaged 56.6% (554/979) with antidepressants vs 64.3% (653/1016) with placebos (χ^2 = 12.3, P = .0004). It seems likely that longer exposure times and larger samples as well as somewhat lower dropout rates with active treatment would tend to favor encountering uncommon suicidal events more among antidepressant-treated subjects. On the other hand, the designs of many of the trials involving treatment-discontinuation-to-placebo among patients recovering from acute major depression might tend to increase suicidal risk with placebo treatment (Baldessarini et al., 2015).

In conclusion, suicides and attempts rather than suicidal ideation are relatively reliable outcomes to be more routinely documented, reported, and compared with other epidemiological studies. Scientific and editorial policies regarding reporting of therapeutic trials should routinely include such data with denominators that include actual exposure times and subject counts in each treatment arm. These recommendations are strongly supported by the present findings, suggesting that such events are surprisingly prevalent even in trials that attempt to exclude currently suicidal participants. They also suggest that special precautions are warranted in monitoring trial participants with major depressive illnesses, especially when antidepressant treatment is discontinued for prolonged times.

Acknowledgments

Statement of Interest

None.

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