

## LETTER TO THE EDITOR

## Suicidal Risks in Report of Reports of Long-Term Treatment Trials for Major Depressive Disorder

R. Dardennes, MD, MS; N. Al Anbar, PhD; S. Divac, PhD; J. Cohen, MD

Faculty of Medicine Paris Descartes, Paris, France (Dr Dardennes and Mrs Al Anbar); Clinique des maladies mentales et de l'encéphale, Hospital Sainte-Anne, Paris, France (Dr Dardennes, Mrs Al Anbar, and Mrs Divac); University of Montréal, Montréal, QC, Canada (Dr Cohen).

To the Editor,  
Baldessarini et al. (2016) recently published a letter re-reviewing their previous meta-analyses of controlled trials of preventive pharmacological treatment of major depressive disorder (Sim et al., 2015). They reported a much higher level of suicidal risks in these trials than those reported in clinical samples of outpatients diagnosed with major depressive disorder and that the overall risk of suicidal events was significantly greater in trial arms involving investigated antidepressant than in placebo controls. Both analyses are of greatest interest, and the authors must be praised for such work to the benefit of the community of psychiatrists and more generally to the benefit of our patients. We were nevertheless surprised to find some discrepancies between published and recalculated data. If some are minor (e.g., recalculated number of person-years in the placebo arm of the Schmidt et al. study (line 5, column 9 is 89.06 instead of published 89.7), some others seem to be more harmful (number of person-years in the treatment arm of Rosenthal et al. study line 12 is 250.24 instead of 2720, resulting in 3.7 suicidal events/100 person-years instead of 0.37; total number of person-years would thus have been 4850 instead of published 2671). More troubling is the last line of the table summarizing totals and means. We found a mean number of suicidal events/100 person-years of 1.32 (with original figure of 0.37 for Rosenthal et al.) or 1.59 (with recalculated figure of 3.7) instead of 1.46 for the treatment arm and 0.63 instead of 0.53 for the placebo arm. When examining the publication of Liebowitz et al. (2010) itself, we found that the number of

suicidal events reported for the treatment arm by Baldessarini et al. (2016) was in fact the number of events in the open-label total population and that, in the randomized phase, zero (0) suicidal ideation was reported in the treatment group (Liebowitz et al., 2010, table 4). Recomputing the number of suicidal events for 100 person-years yielded a mean of 1.26 for treatment vs .54 for placebo.

Whatever the numbers are, finding a higher number of suicidal events in treatment arms than in placebo arms (30 for 2380 person-years vs 12 for 2217, respectively) needs to be explained. The authors judiciously noticed that selected trials were not specifically designed to address suicidal risk and that such trials usually exclude potentially suicidal patients, thus resulting in rarer events and higher risk of chance findings. In fact, the same FDA analyses that showed an increase in the risk for suicidality—suicidal behavior and ideation events—associated with antidepressants in subjects under the age of 25 showed protective effect in subjects of 25 years or older (FDA, 2006a). Further analysis of the FDA data reported specific increase in suicidal behavior for the 18 to 24 age group (FDA, 2006b). Unfortunately, none of the 12 analyzed studies reported neither the number, nor the percentage of adult patients under 25 years both in treatment and placebo arms. This prevented from checking if the unexpected findings of Baldessarini et al. (2016) may have been attributed to differences in age distribution of compared groups. We consider that such secondary analysis of cited controlled studies would be useful and could facilitate further studies in this field.

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Table 4

Study	Treatment	% under 25y		episodes >= 3	Subjects		Ideation		Attempts		Suicide		Total idea+ attempt+suicide		Incidence		events/100 person-years	
		Treatment	Placebo		Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Doogan and Caillard 1992	Sertraline	185	110	0	0	0	0	0	0	0	0	0	0	0	3/216.5	1/128.7	1.39	0.78
Montgomery and Dunbar 1993	Paroxetine	68	67	0	0	0	0	1	0	0	0	0	1	0	1/78.2	0/77.0	1.28	0
Versiani et al., 1999	Reboxetine	145	141	0	0	0	0	2	0	0	0	0	2	0	2/156.6	0/152.3	1.28	0
Rouillon et al., 2000	Milnacipran	104	110	0	0	0	0	5	2	1	10	6	10	10/153.9	6/162.8	6.5	3.69	
Schmidt et al., 2000	Fluoxetine	379	122	1	1	0	0	0	0	0	1	1	1	1/276.7	1/89.7	0.36	1.12	
Thase et al., 2001	Mirtazapine	76	80	0	0	0	0	0	0	0	2	0	2	0	2/74.5	0/78.4	2.68	0
Kornstein et al., 2006	Escitalopram	73	66	0	0	0	0	1	0	0	0	0	1	0	0/106.6	1/96.4	0	1.04
Keller et al., 2007	Venlafaxine	43	86	0	1	0	0	0	0	0	0	0	1	0	0/114.0	1/227.9	0	0.44
Kocsis et al., 2007	Venlafaxine	164	172	1	1	0	0	0	0	0	1	1	1	1/270.6	1/283.8	0.37	0.35	
Kelin et al., 2010	Duloxetine	64	60	0	0	0	0	0	0	0	0	0	0	0	0/103.7	0/97.2	0	0
Liebowitz et al., 2010	Quetiapine	391	385	0	1	0	0	0	0	0	0	1	0	1	0/578.7	1/569.8	0	0.18
Rosenthal et al., 2013	Desvenlafaxine	272	276	5	0	0	0	0	0	0	10	0	10	0	10/250.2	0/253.9	3.7	0
Totals/means	12	1964	1675	7	4	18	7	5	1	30	42	0.01260478	0.00541206	1.26047772	0.54120608			

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