Published in final edited form as:

Curr Psychiatry Rep. 2011 April ; 13(2): 80–81. doi:10.1007/s11920-011-0179-1.

Concerns Over Participant Suicides Prematurely Abort a Clinical Trial of Potentially Significant Impact on Public Health: How Will We Make Progress in Timid Times?

Joseph F. Cubells

Departments of Human Genetics and Psychiatry and Behavioral Sciences, Emory University School of Medicine, 615 Michael Street, Suite 301, Atlanta, GA 30322, USA

Joseph F. Cubells: jcubell@emory.edu

Introduction

Obesity, among the most common “preventable” causes of morbidity and premature mortality in developed societies, fundamentally arises from a mismatch between calories consumed (ie, feeding behavior, which in the rich world occurs in the setting of essentially unlimited availability of high-calorie foods) and calories expended (largely a function of how much or little a person uses weight-bearing musculature [ie, exercise behavior]). Thus, it is useful to view obesity and its adverse cardiovascular sequelae as behavioral disorders. The psychopharmacology of obesity is an important topic from the point of view of pharmacologic treatments aimed at influencing feeding behavior [1], as well as the myriad antipsychotic and antidepressant medications associated with changes in body weight [2,3].

Antagonists at endocannabinoid type-1 receptors (CR1) have shown promise as potential anorexic agents useful in managing obesity. The current report, documenting the abrupt cessation by the sponsor of a large, multinational trial of the CR1 antagonist rimonabant for prevention of cardiovascular sequelae of obesity, is important to the field of psychiatry from a variety of perspectives and raises troubling questions about the willingness of our leaders to take reasoned risks in the service of public health.

Aims

The study aimed to examine the effects of rimonabant on obesity-associated cardiovascular outcomes in obese patients, based on the hypothesis that the medication would promote weight loss and hence reduce cardiovascular risk.

Methods

This large, industry-sponsored study randomly assigned 18,685 obese patients from 42 countries to rimonabant or placebo in a double-blind fashion. Enrollment criteria included large waist circumference (>88 or 102 cm in women or men, respectively), age (>55 years

Correspondence to: Joseph F. Cubells, jcubell@emory.edu.

Trial: Topol EJ, Boussier MG, Fox KA, et al.; CRESCENDO Investigators: Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. *Lancet* 2010, 376:517–523.

Rating: •Of importance.

Disclosure

No potential conflict of interest relevant to this article was reported.

old), history of documented cardiovascular disease (eg, prior myocardial infarction, ischemic stroke, or angiography-documented coronary artery disease), or at least two risk factors for cardiovascular disease (eg, diabetes mellitus, metabolic syndrome, or elevated C-reactive protein). The only psychiatric exclusion criteria were any medical or psychological condition believed by the site investigator to preclude safe participation, or the ability to maintain participation for the duration of the study (planned minimum duration, 33 months). Efficacy end points were a composite consisting of myocardial infarction, stroke, or cardiovascular death.

Results

About 14 months into the study, the sponsor terminated the trial after regulators in Ireland, Germany, and France banned further research in humans with rimonabant. The reason for these regulatory actions and subsequent termination of the trial was that four patients in the rimonabant arm committed suicide, as compared with one in the placebo arm. Although a significantly greater proportion of rimonabant-treated patients experienced neuropsychiatric adverse events (anxiety, depression, depressed mood, or insomnia) (32.3%) compared with the placebo group (22.4%), the authors did not report a statistical analysis of the suicide rate. My own crude analysis (chi-square test, with Yates correction and 1 df, which will tend to overestimate significance because of the small values in two of the contingency table cells) suggests no significant difference in the proportion of suicides between groups ($P=0.375$). Intent-to-treat analysis of efficacy end points revealed no significant differences between the rimonabant- and placebo-treated groups, but power analysis clearly indicated that there was extremely low statistical power to detect any differences so early in the trial.

Discussion

The study confirmed that rimonabant frequently induces negative neuropsychiatric effects, including adverse effects on mood and anxiety, and raises concern that blockade of CR1 can lead to suicide in vulnerable patients who are not properly monitored and managed. Although screening questions for neurological and psychiatric adverse events were included as part of follow-up, it is not clear to what degree suicidal thoughts or behavior were explicitly evaluated. Although details are scant, the authors indicated that some protocol procedures were altered early in the study in an effort to address risk of suicide more carefully; however, insufficient details make it difficult to evaluate those procedures. What is clear is that regulators intervened to stop the work, even over the objection of the study's data safety monitoring boards, according to the authors.

Comments

Although suicide is always tragic, it is important to note that the study population carried known risk factors for suicidal behavior, including poor physical health and advanced age, and the data reported certainly provide no credible evidence of a higher suicide rate in the rimonabant group despite clear support for mood- and anxiety-related adverse events (ie, increased but potentially manageable risk of suicide). The article does not report any details of the suicides, such as methods of suicide or presence or severity of depressive and other psychiatric symptoms in the victims. It would be useful and informative to conduct and publish psychological autopsies on the victims, as these may help identify specific criteria for guiding safer future research on CR1 antagonists.

Undoubtedly, this study is a major setback for research on CR1 antagonists for treating obesity or other indications, because pharmaceutical developers will now hesitate to take on potential liability associated with a class of drugs branded by the current events as "causing"

suicide. The study highlights the increasing challenge of evaluating behaviorally active medications in a highly risk-averse society in which standard medical practice usually underemphasizes appropriate psychiatric evaluation and management. It appears that timid regulators reacted to tragic but inconclusive events to halt a study that could have provided vital information relevant to the treatment of obesity. Such timidity will in the long run probably harm public health.

References

1. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med*. 2005; 142:532–546. [PubMed: 15809465]
2. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. *J Clin Psychiatry*. 2010; 71:1259–1272. [PubMed: 21062615]
3. Tarricone I, Atti AR, Salvatori F, et al. Weight gain in antipsychotic-naïve patients: a review and meta-analysis. *Psychol Med*. 2010; 40:187–200. [PubMed: 19656426]