A Mirror-Image Trial or Smoke and Mirrors? Phase 3b Study on Digital Aripiprazole

To the Editor: In November 2017, the US Food and Drug Administration approved a version of a second-generation antipsychotic, aripiprazole, embedded with a sensor (AS; Abilify MyCite) despite a clear lack of rigorous evidence of benefit,[1] with no controlled trial. Only 3 non-comparative uncontrolled cohorts were found. None provided data on any clinical efficacy outcome.

The authors of a recent phase 3b study published in this journal[2] claim to have addressed this gap for adults with schizophrenia. However, the flaws in design and reporting of this study provide a false impression of the efficacy of AS, compounded by the uncritical comment published concurrently.[3] We offer the following methodological and ethical critique.

First, this uncontrolled cohort compares "retrospective" and "prospective" follow-up of the same patients, with no randomization, which is very low in the hierarchy of evidence, especially when a randomized controlled trial comparing AS versus aripiprazole is feasible and desirable.

Second, results are reported for only a subset of patients. The analysis population is defined as "participants who completed the month 3 visit or had ≥80% of their study medication ingestions recorded by the AS system during prospective months 1–3."[2(p e3)] This is not a modified intention to treat (mITT), as stated, but rather a per protocol analysis including 113 of 277 enrolled patients (41%). The others were withdrawn, were lost to follow-up, or failed to take medication. Attempting to draw conclusions about medication adherence when fewer than half of the participants remained in the study flies in the face of common sense. Additionally, 50 patients were excluded from the analysis based on results of an interim analysis. Both post hoc exclusions and interim analyses are best avoided, especially in a single-arm trial.

Third, the study compares past hospitalization rates when patients took standard oral therapy versus when they used digital aripiprazole. However, the main selection criterion (≥1 inpatient psychiatric hospitalization in the preceding 48 months) overlaps with the primary outcome definition (difference in proportions of participants with ≥1 inpatient psychiatric hospitalization between prospective and retrospective months 1–3). Regression toward the mean during follow-up is expected to artificially generate lower hospitalization rates. Therefore, the difference observed on the primary outcome reflects bias rather than a genuine efficacy of digital aripiprazole. This is confirmed by the high "efficacy" found in patients with poor adherence or lost to follow-up at 3 months, obtained by subtraction of the ITT and mITT samples. In this subsample of 164 patients, there were 3 (1.8%) hospitalizations in the 3-month prospective period vs 15 (9.1%) in the retrospective period.

Such major flaws in design, conduct, and analysis and the central involvement of the sponsor are features of trials driven by marketing interests.[4] Small numbers of patients were recruited from 58 study sites over most American states. For such a common disease, this suggests a "seeding" trial[5] done to familiarize doctors with use of a drug rather than a scientific study.

Digital drugs raise ethical issues,[6] especially about coercion. Members from disadvantaged communities are more frequently subjected to involuntary and coercive psychiatric treatment. Balancing these potential harms deserves adequate evidence before recommendations of AS are made.

Dr Reuteman-Fowler was shown this letter and declined to reply.

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Florian Naudet, MD, PhD[a,*]
André Gillibert, MD, PhD[b]
Barbara Mintzes, PhD[c,d]
Alain Braillon, MD, PhD[e]
Lisa Cosgrove, PhD[f]

[a]Univ Rennes, CHU Rennes, Inserm, Centre d'Investigation Clinique de Rennes (CIC1414), Service de Pharmacologie Clinique, Institut de Recherche en Santé, Environnement et Travail (Irset), UMR S 1085, EHESP, Rennes, France

[b]Department of Biostatistics, CHU Rouen, Rouen, France

[c]Faculty of Medicine and Health, School of Pharmacy and Charles Perkins Centre, The University of Sydney, Sydney, New South Wales, Australia

[d]School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada

[e]Retired senior consultant, Amiens, France

[f]Counseling Psychology Department, Applied Ethics Center, University of Massachusetts-Boston, Boston, Massachusetts

**Corresponding author:* Florian Naudet, MD, PhD, Clinical Investigation Center (INSERM 1414), University Hospital, 2 rue Henri Le Guilloux, 35000 Rennes, France (floriannaudet@gmail.com).

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ORCID: Florian Naudet: https://orcid.org/0000-0003-3760-3801; André Gillibert: https://orcid.org/0000-0002-0797-1817; Barbara Mintzes: https://orcid.org/0000-0002-8671-915X; Alain Braillon: https://orcid.org/0000-0001-5735-9530; Lisa Cosgrove: https://orcid.org/0000-0003-3101-5726.

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