SHORT PERSPECTIVE

The Science of Doing Right: Reflections on a Global Mental Health Advocacy Project

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BACKGROUND

In July 2013, the World Health Organization (WHO) approved an application submitted by Mount Sinai physicians, Dr Craig Katz, Dr Anna Rosen, and Dr Hiwot Woldu, and medical student Jasleen Salwan to add risperidone to the Essential Medicines List. Initiated in 1977 and updated every 2 years based on applications for revisions submitted by parties outside WHO, the list guides drug policy in developing nations around the world. Although it is not binding, it helps government officials as well as external donors set funding priorities.

WHO's approval of the Mount Sinai team's application marked the first addition of an atypical antipsychotic to the list, addressing a major neglected area of global health. It is hoped that it will be followed by many more victories for underserved psychiatric patients across the globe.

 Annals of Global Health 2014;80:80-82

Conventional wisdom dictates that we draw a bright line between inquiry and advocacy. For research to be considered scientific—and to avoid the crushing label of "pseudo-scientific"—it must be unbiased, objective, and as detached as possible from the very people to whom its findings are most relevant. A scientific investigation, we insist, must aim to explore rather than to serve. As a medical and public health student, I used to find this doctrine arbitrary and frustrating. But when I was invited to conduct research that would translate directly into advocacy, I realized that I needed the principles of scientific inquiry to provide an ethical grounding for my work. In defining what to advocate for, it would prove prudent to erase my preconceptions about my target population's needs. It was only when such impartiality was no longer expected of me—indeed, when bias was not merely permitted, but practically demanded—that I recognized the value of approaching advocacy work with a scientific mindset.

From my first term at the Icahn School of Medicine at Mount Sinai, I found myself navigating complex waters: I was struggling to comprehend the world of getting published. Residency match was more than 3 years away, but many of my peers were already vying for first authorships. My first instinct was to jump into the competition, but on further reflection, I questioned whether all of these research endeavors would truly benefit patients on a large scale. With so many journals and articles out there, could any one study really be a game-changer for patient care? Impact factors aside, what effect could one have by joining the ranks of those who had gotten published? What I longed for was a project that could in itself effect policy change, something that would not just sit in an archive, hoping to be noticed by someone with the power to make a difference.

Sooner than I expected, I was presented with precisely this kind of opportunity. In the fall of my first year, my faculty mentor at Sinai, a psychiatrist who had spearheaded numerous initiatives in global mental health, invited me to work on an application to add the atypical antipsychotic risperidone to the World Health Organization's (WHO) Essential Medicines List. Although not binding on any country governments, the list influences drug policy at national and institutional levels around the world. At the time I joined the project, the list contained only first-generation antipsychotic medications; none of the atypical drugs, despite their established comparative efficacy and safety, were included. During several of my mentor's projects abroad, he had spoken with mental health professionals who lamented the shortage of risperidone for patients who desperately needed it. I saw joining the project team as my chance to use research to the clear benefit of an underserved patient population. I was eager to free myself of the suffocating rigidities of lab protocols and statistical models in favor of a hands-on, get-out-there-and-do-something approach.

2214-9996/

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No financial support was received for this manuscript. The author has no conflicts of interest to disclose.

http://dx.doi.org/10.1016/j.aogh.2014.04.009

Given my outlook, I was disheartened when I first read the application instructions and took them at face value. The WHO required a rigorous review of the literature on every drug presented for its consideration. Our submission would need to provide comprehensive information on the effectiveness, safety, and cost-effectiveness of risperidone relative to other drugs "within the pharmacological class or therapeutic group." Making a case for risperidone vis-á-vis typical antipsychotics would be facile, but to obey the application instructions to the letter would require comparing risperidone to a host of other second-generation antipsychotics across multiple dimensions. Netting out the advantages and disadvantages in each category of risperidone, olanzapine, clozapine, quetiapine, and others, who was to say which would come out on top? Several of my mentor's colleagues in developing countries had expressed a specific need for risperidone. I wanted to honor their requests, but if I had to adhere strictly to the WHO's guidelines, this would prove challenging.

When I looked at successful past applications for various other drugs, however, it became clear that the WHO did not actually expect such scientific thoroughness. Although the instructions listed 15 required components with numerous subcomponents, the WHO had previously approved multiple submissions that fell short of 15 pages. Alarmingly (but not surprisingly), the shorter submissions tended to ignore the WHO's instructions to specify the search strategy used to identify studies on the effectiveness of the drug. Regarding safety, one successful past application took on a worryingly assured tone, asserting that the drug's adverse effects were "not significant" but supplying only a vague description of how that conclusion was reached.

At first, I could not help but feel relieved. Not only did it seem that I could avoid the tediousness of going through hundreds of articles with a fine-toothed comb, but I could embark on this project with a sense of certainty about the desired end. But before we even began, my mentor warned our team that in order to do right by the patient population we intended to serve, we must avoid bias. "If [the best drug] is not risperidone, we won't apply for risperidone," he said firmly. Instead, we would come together after completing our designated research tasks and decide which atypical antipsychotic to submit to the WHO. I admired his resolve, but I still feared that if we approached the literature review completely *tabula rasa*, we would end up going in circles.

When my initial PubMed searches yielded more than 500 results, I might have been especially tempted to focus on those studies that pointed to the advantages of risperidone. Instead, something about the enormity of the task before me elucidated the wisdom of my mentor's perspective. Frustrated as I was with the rigidities of scientific methodology, one of its truisms had been deeply impressed on me: the larger the pool, the less acceptable any cherry picking. With so many articles to choose from, it would be all too easy—and all the more unethical—to deceptively build a convincing case for risperidone. Recognizing that countless hours doubtless went into building such a rich knowledge base, giving the existing research anything less than a meticulous examination would be both insolent and unscrupulous.

So we were meticulous. As my colleagues and I pored through abstract after abstract on PubMed and Cochrane, I forced myself to embrace the inevitable confusion that resulted. As I had anticipated, it proved difficult to weigh the relative importance of each factor that the WHO took into consideration. At first blush, efficacy might seem of the utmost importance, but the drug that appeared the most efficacious—clozapine—also carried the most serious side effect profile. Given that many of the intended beneficiaries of our work lived in low-resource communities, cost-effectiveness also needed to be given substantial weight, but most studies of cost were conducted in developed countries and thus had questionable applicability to our target population. Rather than get overwhelmed, we redoubled our thoroughness, patiently allowing the project to stretch on from the summer into the fall. In November, when we combined our findings into a single document, it totaled more than 60 pages.

With our research complete, we weighed whether to propose risperidone or another atypical antipsychotic. All of us agreed that the literature did not point decidedly to risperidone—but it did not favor any other drug, either. Ultimately, we came back to risperidone because it carried fewer risks of weight gain than its closest rival, olanzapine. "We obviously don't want to add diabetes/metabolic issues to the many problems developing countries already have," one of my colleagues pointed out in an e-mail.

Still, we were determined to avoid overstating the benefits of risperidone. Our mentor advised that we "let the literature speak for itself." In our submission to the WHO, we explicitly acknowledged that "in comparisons of risperidone with other atypical antipsychotics, the available data is not conclusive." Even in the introduction, where we summarized our reasons for proposing risperidone, we used qualified language. We characterized risperidone not as a unique drug but rather as one of a class of medications that ought to be represented in the Essential Medicines List. Within that class, we added, risperidone offered a "good balance" of efficacy, safety, cost-effectiveness, and other considerations. Comfortable with this truthful and balanced approach, we waited for a response from the WHO.

The WHO wrote back to us with a "request for clarification," with comments embedded in our submission document. It was obvious that to effectively clarify our reasons for proposing risperidone, we had to be willing to use more decisive language. In one comment, the committee suggested a place where we might insert a paragraph detailing the comparative

advantages of risperidone. They also urged us to draw more inferences from the data we had: in one instance, they inserted the comment, "and is therefore?" at the end of a sentence describing risperidone's advantages for the treatment of bipolar disorder. Clearly, letting the data speak for itself was not going to suffice.

In following the WHO's suggestions, I felt rather uneasy. When I first joined the project, I had envisioned myself arguing passionately, (and, I hoped, persuasively) to take a first but significant step toward getting risperidone to people who needed it badly but lacked the political voice to demand it. My goal was specific, and I had no intention of wavering from it. But as my research grew more extensive and more complicated, I had come to understand the project as a scientific inquiry rather than as an opportunity to stand on a soapbox. By approaching the work with the mind of a researcher—open and free of assumptions—I would be a more honest advocate.

Ultimately, we decided that advocating with slightly stronger language than we had intended was better than accepting the status quo. We submitted a revision, and risperidone was approved for inclusion in the 18th WHO Model List of Essential Medications. It was a proud accomplishment, but my self-satisfaction would not go unchecked. This August, when the attorney general of Kentucky sued Johnson & Johnson for concealing risperidone's adverse effects, I began to second guess my team's choice. Had we missed something in our review of the literature on safety? Did the studies we examined favor the pharmaceutical industry's interests? It is too early to answer these questions, and I remain convinced that the list's inclusion of an atypical antipsychotic is an improvement. Still, my experience taught me that scientific rigor confers a certain humility on advocacy work. In determining how best to serve a patient population, we can never be absolutely certain that our goals are the right ones. Like researchers immersed in the infinite pursuit of scientific truth, we must continuously question our judgment, repeatedly fine-tuning our moral compasses as we seek to understand how to do right by our patients.