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Discussion

Alzheimer Research Forum Live Discussion: Can We (Should We?) Develop "Smart Drugs" to Stave Off Age-Related Memory Loss?

(*http://www.alzforum.org/res/for/journal/transcript.asp?LiveID=173*)

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Note: Transcript has been edited for clarity and accuracy.

Carrolee Barlow: Should investigators develop cognition-enhancing drugs to stem a process that occurs "normally" (i.e., aging)? Could Rusty comment on the current lack of approved treatments for age-associated memory impairment (AAMI)?

Russell Katz: There are not any approved treatments for AAMI, but only presumably because industry seems to have abandoned the project. As far as I know, nothing worked, but I do not know exactly how many studies were completed. The regulatory requirements were more or less worked out with the sponsors.

Gretchen Reynolds: I have a question for any of the participants: if exercise becomes an accepted way to decrease the severity of cognitive decline, is it reasonable to have doctors start "prescribing" exercise? And if so, not to be facetious, should running shoes and gym memberships become reimbursable from insurance companies?

Hank Greely: Gretchen, yes, at least in terms of reimbursement. In fact, some health plans are subsidizing exercise-related expenses. (Whether it works in the sense that it gets people who would not exercise to actually do it, consistently and for the long run, as opposed to subsidizing those who would anyway, that remains to be seen.) There is no "prescription," though; there is nothing to order a pharmacist to prepare.

Scott Small: Gretchen, I agree this is reasonable, particularly for old and "frail" individuals who have other comorbidities (i.e., arthritis, heart disease). Thus, I think exercise would be best thought of as "physical therapy" and therefore reimbursable.

Hank Greely: To follow up more with Gretchen, whether or not something is covered by health insurance (or an HMO) is, initially at least, a matter of the insurance contract (affected to some extent by regulatory requirements). An insurer can certainly add that kind of benefit if it wants – and when employers think

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the benefit will be cost-effective for them, you will see it offered.

Patricia Heyn: About exercise: we do not have a guideline/protocol in place. Yes, in general, physical activity has been shown to support neuroprotection and enhancement, but what should be the prescription, the dose, intensity, and even mode? There is still much more work to be done in the activity-induced cognitive enhancement research area. We need to study behavior adherence and motivation, as well.

Hank Greely: Rusty, do you see any good way to handle the risks of off-label use? What if lots of teens and 20-somethings were using a drug that had been tested only in people over 50? If a good treatment is developed for memory decline in older people and younger people start using it widely without any clinical trials, I would be worried about safety.

Gabrielle Strobel: In thinking about off-label use of such future drugs, is this not a broader problem of the FDA's resources to police inappropriate off-label use? Off-label use that draws criticism from clinicians and the Alzheimer's Association comes up in AD treatment from time to time, but to my knowledge has not prompted action by the FDA.

Robert McArthur: There appears to be a tacit acceptance that magic white powders will magically, or with a little training, "enhance cognitive abilities" that can transform middling intelligence to super bright in a manner analogous to taking steroids to enhance physical abilities. Where is the evidence for such an assumption? The drug industry has been trying for decades now to provide Alzheimer's patients with such a magic powder and has succeeded only in tweaking memory, attention, and other cognitive processes of such patients. These cognitive-enhancing drugs have been tested and characterized using specific testing conditions. Even if one is able to demonstrate a statistically significant improvement in performance in a more general population setting, i.e., during school exams or aptitude tests, what is the evidence that administration of these compounds/drugs will have long-term effects on presumably enhanced cognition?

Gabrielle Strobel: Robert, to clarify: Scott Small's presentation today focused on biological, mechanistic differences between cognitive aging and AD. These would provide the basis for drug discovery and lifestyle intervention. Regarding future anti-cognitive aging drugs, Dr. Katz said that the FDA would require data to show not only that such drugs have statistically significant effects in specific testing conditions, but also that they are clinically meaningful to people. We are not focusing on off-label use of current AD drugs by the young and healthy in this hour. So off-label use of those drugs is a future concern, not the goal. Does that address your concern?

Hank Greely: Gabrielle, I agree that off-label use is not the goal of those developing these drugs, but I do not think it is only a future concern. It is something we should think about – I believe – whenever a new drug is approved that has the potential for substantial off-label use. Unfortunately (I think), the law does not give the FDA much control over off-label uses except through regulation of marketing. Robert, the basis for my assessment that there is a "reasonable chance" such things will be developed is the incredible revolution in our knowledge of the human brain. Drugs that significantly enhance cognition may or may not actually come to pass, but they are not a crazy idea.

Robert McArthur: Having worked for many years on pharmaceutical drug discovery for the treatment of AD, I, too, would not say that it is a crazy idea. However, one does become concerned with the assumption, even within the industry, that our "cognitive enhancers" will do good things not only for the cognitively impaired but also for the normally functioning individual. The effectiveness of these compounds is yet to be shown.

Gabrielle Strobel: Robert, what do you think about aging and age-related decline? Would that seem more acceptable to you? That is really the specific aspect to this discussion today. Rusty, about whether the FDA could use more authority to curtail off-label use where inappropriate: would you welcome that?

Russell Katz: Gabrielle, I am loath to ask for more authority in this area, because we get into the practice of medicine and that is very problematic from my point of view. I think it depends on each case, but I think primarily our job is to approve drugs that are safe and effective for a particular use, and be truthful in labeling about what we do know and do not know (where appropriate). I think there are many issues that need to be considered before we tread heavily onto the practice of medicine.

Hank Greely: Rusty, that is a wise answer, certainly politically but also prudentially. But it is worrisome when drugs become very widely prescribed (and, when widely available by prescription, become easily accessible on a black market) for people and conditions other than those for which they have been tested. I respect doctors highly (I am married to one), but I do not trust the country's 800,000 doctors always to do the right thing. I think the FDA might consider requiring, or encouraging, broader testing for drugs where off-label use seems likely. But I know this is tough – in terms of legislative authority and political power.

Gabrielle Strobel: Hank and Rusty, and all, it seems to me simply as a reader of newspaper coverage of these issues, that patients' and doctors' not adhering to a drug's label and safety restrictions causes at least some of the public controversies around drugs – unintended side effects, drug withdrawals from market, lawsuits. Given all this, it seems to me that curbing unsafe off-label use would have benefits, certainly with drugs that act in the brain and therefore are of perhaps heightened concern. No?

Russell Katz: Gabrielle, I cannot say what folks will do in this regard. I agree that doctors may prescribe inappropriately. We certainly spend a fair amount of time encouraging companies to develop drugs for populations that we know will be (or are being) treated off-label. There already are some provisions in the law that allow us to require studies. For example, we can require studies in pediatric patients if the disease for which it is approved in adults exists in kids. And recently the law did give us the authority to study certain conditions if we become aware of a new safety signal (this is very recent), so we do have some authority that we did not previously have, but this is quite new.

Gabrielle Strobel: Hank, you raised the issue of fairness and access with such drugs in your audio presentation (http://www.alzforum.org/res/for/journal/detail.asp?liveID=173) – is it much different than the broader issue of privilege in society in general? Wealthier people have advantages in many different arenas already, certainly including health and longevity. Anything specific to this type of drug that strikes you as worth thinking about?

Hank Greely: Gabrielle, that is a great point. The rich can buy lots of cognitive enhancers, like good schools, tutoring, etc. I do not think this is fundamentally different, but it is one more, cumulative unfairness – and, like many things, is probably more addressable before it becomes widespread rather than after. There really are two fairness questions, by the way – the broad, social "rich/poor" or "well insured/poorly insured" fairness issues, and individual fairness issues – in this case, maybe contestants on *Jeopardy* would be the clearest example, though job performance broadly could be implicated.

Gabrielle Strobel: Scott, can you say anything about the kind of compound discovery based on your dentate gyrus findings that your laboratory is undertaking?

Scott Small: Gabrielle, we are still in the "preclinical" stages, namely, attempting to identify the molecular defects that "cause" age-related dentate gyrus dysfunction. As I mentioned, one of the lead hits is molecules that relate to histone acetylation. This is potentially interesting because there are a number of available drugs that might correct this problem. We are currently testing to see whether they "rescue" age-related dentate gyrus dysfunction.

Gabrielle Strobel: Scott, I wonder, how long in the aging and dementia processes does the separation between the entorhinal cortex and the dentate gyrus hold? As people progress in AD, pathology and volumetric shrinkage spreads to other brain areas. Can one really distinguish based on hippocampal subareas except in the very earliest stages of both processes?

Scott Small: Gabrielle, from a clinical perspective, once AD progresses it actually is not very difficult to distinguish AD from aging. It is nearly trivial. Although your point is well taken, the anatomical differentiation "game" is most easily played at early stages.

Gabrielle Strobel: I was wondering in terms of developing a cognitive aging drug, how you can make sure that you keep trial groups separate if indeed trials have to be very long. Because having the wrong people (e.g., MCI "contamination" in your cognitive aging group) in your trial arms might make it harder to get a significant efficacy signal for the drug. On that issue, perhaps high-resolution MRI would be helpful to keep folks with MCI/incipient dementia out of trials? I am saying that because in past MCI trials, clear delineation of the trial arms has been a problem.

Scott Small: I see . . . One thing about clinical trials: I do think that treating a "sick cell" will be easier than

treating a dead cell. This, as you know, is the great promise of "functional imaging." Not only distinguishing from aging, but earlier detection of AD, before the onset of rampant cell death.

Gabrielle Strobel: Rusty and all panelists, the drug Alzhemed, which is a derivative of an amino acid sold in health food stores and infant formula, had unapprovable Phase 3 data and was widely considered to have failed formal drug development. It is now being marketed in Canada as Vivimind for exactly what we are talking about today – age-related memory loss. It is a non-FDA-approved supplement that claims to be scientifically proven to protect memory function. Given this experience, is it not likely that other developers of cognition drugs will opt for this route to the market right away, rather than go through the FDA process, especially if trials for a normal population have to be large and long, i.e., expensive?

Hank Greely: Gabrielle, the dietary supplement loophole (today's "patent medicine," I think) is particularly plausible for enhancement, as dietary supplement makers are not allowed to make disease claims (treatment of heart disease) but only structure and function claims (improves cardiovascular health). "Improves cognitive performance"/"improves memory" is a classic structure and function claim. So if the molecule involved is found in something that someone, somewhere, sometime, has been eaten as a food, I would worry about an almost totally unregulated influx of dietary supplement cognitive enhancers...and, in fact, you can already find many on sale at health food stores. The good news, I guess, is that, thus far, they probably do not work.

Gabrielle Strobel: Hank, Rusty, and all, along this vein, there is also a product called Axona by a company named Accera. This started out in regular Phase 1 and 2 trials, but rather than moving on to Phase 3 is going to be marketed soon as a so-called "medical food." Is that basically a middle route between formal drug approval and no regulation at all for a dietary compound with memory function claim? Where basically the FDA grants a safety designation but no efficacy designation, in other words "will not do harm but not proven to help?"

Russell Katz: These products are foods to be administered under the auspices of a physician intended for specific dietary management of a disease that requires "distinctive nutritional requirements." This is intended to be a narrowly defined category. The last thing I am is an expert in this area, but it seems that these products have to be foods (i.e., have some nutritive value), and the patients for whom they are intended have to have some problem managing ordinary food. It does not appear that products that are not otherwise foods would qualify as medical foods, and it does not look like medical foods can make claims like cognitive enhancement. Dietary supplements are defined specifically in the law, and are allowed to make "structure/function" but not disease claims (e.g., they can say they improve memory, but not that they treat AD), and these claims are not reviewed by the Agency prior to their being permitted.

Mark McInerney: I have a question for Dr. Katz: there is a high probability that any new "cognitive enhancer" will probably be introduced through a proven regulatory pathway (like the one for adult ADHD). Would a drug featuring a new mechanism, like nicotinics, be subject to a cognitive enhancer-type safety hurdle (i.e., long trials with large numbers)?

Russell Katz: I am actually not so sure that there is a high probability that a cognitive enhancer would first come in through a more traditional route, but be that as it may, I believe that any compound that came in for such a "cognitive enhancer" in otherwise "normal" people would probably be subject to what Mark refers to as the "cognitive enhancer-type safety hurdle." Certainly, a new mechanism may raise some new issues, but, in general, it is the claim that is being sought (and, of course, the degree of benefit seen), as well as any issues specific to the proposed population, that dictate the safety requirements. Even if the drug is already approved for some indication, if the new proposed indication markedly expands the population that would be exposed to the drug, new safety requirements appropriate to the new claim/population would be imposed (of course, in this circumstance, the previously accrued safety data are likely to be of some use, assuming the population for whom it is already approved bears some likeness to the new proposed population, so that the safety data gained in the old population would be relevant for the new population).

Patricia Heyn: I hope we will find more opportunities to further discuss these interesting topics.

Gabrielle Strobel: We are nearing the end of our hour. Let me thank you all for coming and driving such a lively conversation.