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Dear SMRB Members,

Thank you for the opportunity to provide written comment on the detailed review provided by the SUAA Working Group. As the meeting date of the SMRB coincides with an important meeting of the international community on alcohol problems, ISBRA, many of the leaders in the field are at that meeting in Paris, either giving presentations or participating, and have only this venue to respond by written comment in the very small hours of the morning.

I agree that the SUAA Working Group should be congratulated on their diligent and hard work, and that their general conclusion that the status quo is not optimal is appropriate. The more fundamental question, however, is how to create optimal synergy between NIAAA and NIDA to provide the best science that can be applied to the prevention and treatment of all substance-use-related disorders.

My view is that a functional merger would achieve the goal of creating the optimal synergy in a focused manner that conserves resources, builds upon clear examples of success, and avoids the significant risks of a highly complicated, expensive, and untried attempt to do this through a structural process. From this vantage point, there are five important veins of consideration that need to be highlighted.

First, the promotion of the overarching view that all addictions simply fall within a known addiction circuitry of reward is rather overstated, and cannot be viewed as the "theory of everything" related to addiction. Notably, whilst this reward circuit appears to have support at the level of acquisition of addictions, once the disorder is established this is no longer necessarily the case. Indeed, advances in the neurosciences show clearly that circuits outside this traditional reward circuit become increasingly important with an established addiction, and that these vary for different drugs of abuse, including alcohol. Indeed, new knowledge on these neuromodulators of the addiction process shows that small molecules and neurohormonal circuits are particularly important, especially in the case of alcohol. Therefore, the addiction circuitry for alcohol has some overlap with that for other abused drugs but is far from being the same. Furthermore, despite several decades of this concept of a singular central addiction circuitry, there is no single

established medicine in humans that cuts across the treatment of all these disorders. Curiously, with regard to specific addictions, for example with opiates, we have not been able to develop any cogent non-opiate-related treatments based on this addiction reward theory. What appears to be emerging is that the neuropharmacological differences between alcohol and other drugs might actually hold the key as to the success of medications development for these different disorders. For example, with respect to alcohol, non-brain systems related to metabolism appear to play an important role in its intake. Hence, an identical neuroscientific approach to the treatment of alcohol dependence is unlikely to generalize well to that for drug dependence. Thus, a structural merger of institutes based upon a narrow focus on the addiction circuitry will not provide a comprehensive scientific understanding or treatment option for all addictions that we currently seek. Indeed, much more is likely to be gained by developing themes of collaborative research and a functional blueprint between the two organizations.

Second, the global perspective of the scientific and clinical communities points to a functional rather than a structural merger of the two institutes. Whilst it was emphasized that there are two separate scientific meetings, one for alcohol abuse and another for drug abuse in the U.S., this actually very much represents the global perspective. The global community recognizes the clear distinctions between these disorders and is organized as such. For instance, the end-organ focus of NIAAA that would have to be jettisoned to other NIH-related institutions is actually at the very core of the focus of the global scientific community for alcohol-related diseases. Indeed, these alcohol meetings around the world include as many liver experts, cancer specialists, and general physicians as those specifically related to the treatment of alcohol dependence. That important connection would be lost in a structural merger, thereby setting back important work and advances in liver disease, cancer prevention, and fetal alcohol syndrome (one of the most common acquired congenital disorders). With respect to training, whilst it is important to teach overlap, it would not be feasible for any trainee to become an expert across all these fields, interact with all the specialists, and attend all the important scientific meetings. Focused training in these individual specialties would best protect the respective fields of alcohol and drug addiction, with attention to the points of overlap.

Third, there are clear examples of functional mergers within the NIH that have worked well but barely any clear examples of a successful structural merger of this scope and size. In these pressing economic times, there needs to be clearer understanding of the costs associated with the proposal of a structural merger, and I do not think we can operate as if there is an endless supply of funding. Have there been a feasibility analysis and a cost estimate? Has there been an analysis, even at a cursory level, of whether the large sums of money, which could reach billions of dollars to structurally merge these two institutes with uncertain results, could be best used in a targeted approach toward creating important fusions in projects with clear scientific objectives and goals? Would it not be prudent fiscally to try first a functional merger along the sequence provided by the SUAA in its report that can be more easily managed, monitored, and shaped? Has there been any planning given to personnel wastage that might ensue, the cost of retraining, the colossal administrative work in identifying new leadership and leadership structures, and the formidable task of how to manage infrastructure across different states? Also, has there been consideration of the fact that the price of failure for a large structural merger—which would conservatively take up to a decade to be actualized fully—would be unacceptably high, both in economic and in human terms? Clearly, defined functional goals and themes within two separate institutes that can be managed appropriately within a known framework would render the optimal and most feasible outcome. At the very least, it would lay the necessary foundation and guiding principles for the consideration of a possible structural merger in future years as the institutes become closer.

Fourth, the data provided within the SUAA report also can be interpreted differently. Indeed, the report highlights the closer interaction between drug abuse and mental disease, which would point to a merger between NIDA and NIMH. If so, why has this not been considered even from the point of a preliminary investigation to increase the balance of the present report?

Fifth, I was puzzled by the statement that industry was not interested in developing drugs to treat drug addiction as a potential reason in favor of a structural merger. This is not quite the case. Indeed, industry is involved with developing medications for the treatment of opiate addiction where there has been clear success in identifying efficacious treatments. The same observation is evident for treatments related to nicotine dependence. Hence, if NIDA were to be successful with finding an efficacious medicine to treat stimulant dependence, it is most likely that industry would be interested in exploring that potential. Clearly, there are important lessons that can be learned from cross-talk between the medications development programs of both institutes, but since even the clinical endpoints are not the same for medications development, the concept of "one size fits all" would not work well.

In sum, I thank you for the time to read this note, which would have been shorter given more time, and for your thoughtful consideration of this most important matter.

My best wishes for the meeting,

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