2013 IACC Strategic Plan Update – Question 4 Draft

"Which Treatments and Interventions Will Help?" - Volunteer drafter – Tom Insel

Introduction

The aspirational goal for Question 4 is to "Development interventions that are effective for reducing both core and associated symptoms, for building adaptive skills, and for maximizing quality of life and health for people with ASD." A review of the state of the science in 2009[1] noted that many treatments were in use, but little rigorous evidence existed to support their safety or efficacy. At that point, the Committee identified intervention research needs from two quite different approaches. One approach, dependent on progress in Questions 2 and 3, called for novel, targeted interventions based on an understanding of the molecular mechanisms of ASD. The other approach, related to Questions 5 and 6, called for rigorous studies to test the efficacy and safety of interventions that were already in wide use, including behavioral and complementary medicine approaches.

The *2009 Strategic Plan*, included six objectives, with an additional six objectives (including some with multiple parts) being added in the revisions in 2010 and 2011. Altogether the most recent version of the *Strategic Plan* recommended a wide range of studies, including 19 randomized clinical trials, 20 model system studies to identify treatment targets, and one workshop. The total recommended budget was $283.2M across all 12 objectives.

Progress

The *2011 - 2012 IACC Portfolio Analysis* reviews ASD projects funded by both government agencies and private organizations from 2008 to 2012. Based on this analysis, the cumulative investment from 2008 to 2012 was $309M. Focusing on 2009 – 2012, the period after publishing the *2009 Strategic Plan*, the total investment was $255M. This means that on average, the yearly investment during this period was 18% higher than in 2008 ($54M). It is important to note that from 2009 to 2012, roughly 90% of the investments assigned to Question 4 align with one of the 12 objectives, which addressed gap areas in the portfolio, and about 10% of the objectives addressed core/other activities that were not specific to any objective and may represent emerging areas of research not yet captured by the *Strategic Plan* objectives.

Because most clinical trials require several years for completion, the snapshot of 2012 may be helpful for assessing the current portfolio of activities relating to treatments and interventions for ASD. There were 269 projects funded in 2012 at a cost of $64M, with 240 projects distributed among each of the 12 objectives and 29 projects ($3.9M) assigned to core/other activities, thus demonstrating the broad range of research currently taking place in this area.

The research portfolio related to four of the objectives was considered to have met the recommended budget and number of projects, including those that called for randomized controlled trials (RCTs) addressing co-occurring conditions, development of model systems, early intervention trials, and studies on interventions for non-verbal individuals. Eight objectives had their funding goals partially met. These objectives included testing safety and efficacy of interventions, investigating biological signatures, health promotion, medication trials, interventions to prevent recurrence in siblings, medications to treat co-occurring conditions,

community studies evaluating intervention effectiveness, and a workshop on clinical subtypes and treatment personalization (partial because a workshop that took place only partially met the requirements set out in the objective).

As noted above, there were 269 active projects in 2012 that were responsive to Question 4, with the large number of studies reflecting the wide variety of research into treatments and interventions for ASD. Despite the numerous avenues currently being pursued, however, many funded psychosocial, behavioral, medication and other biomedical intervention trials are being conducted with small budgets, suggesting that these projects are under-powered to provide the needed evidence for efficacy or safety. s. It is important to note however, that some of these projects are exploratory, and thus are appropriately funded with smaller budgets as an initial step, prior to larger scale investment if the strategies yield promising results. Additionally, the absence of therapeutic targets or consensus outcome measures makes interpretation of positive or negative results difficult, although as this field matures and the research moves forward, this problem is likely to resolve.

Again, reflecting the very early stage of intervention development for ASD, nearly one-third of the budget aligned with Question 4 was invested in one objective: the standardization and validation of model systems to identify molecular targets or circuits for treatment development. Several objectives that addressed the assessment of current treatments received less investment. In particular, testing the safety and efficacy of widely-used treatments ($1.3M in 2012) and studies of interventions for either secondary conditions ($1M in 2012) or co-occurring conditions (less than $1M in 2012) received relatively little investment, indicating an need to increase work in these areas. In developing the Strategic Plan, the Committee emphasized the need for research to develop treatments for those most severely disabled by ASD, including those who are minimally verbal. Encouragingly, examination of the research portfolio showed strong growth in research on minimally verbal ASD, reflecting the interest of the research community in seeking to develop new approaches to help this population. Continued investment in this area will be vital to progress.

Overall, there has been considerable activity on Question 4 since the launch of the *IACC Strategic Plan* in 2009. While the overall financial investment roughly matches and, in many areas, exceeds the recommendations put forth in the *Strategic Plan*, it is too early to assess the impact of these investments. Although clinical trials of pharmacological interventions for core symptoms of ASD are now underway, they require several years for completion, analysis, and reporting, so to-date there are very few published findings[2]. Preclinical studies, which have a shorter delivery time, have however, yielded some remarkable insights, especially for mice with mutations that model syndromic forms of ASD, such as Fragile X or Rett[3,4]. In affected mice, treatments reverse the syndrome both in development and in adulthood[5a]. While these studies give hope, the relationship of syndromic autism to idiopathic autism (autism of unknown cause) is not clear. Furthermore, in many areas of neuroscience, efficacy in mice has not translated into efficacy in human patients. In summary, while there have been significant advances in the areas of genetics and neurobiological studies, the advances have not yet been translated into a full pipeline of molecular, cellular, and systems targets for interventions. The recent interest of pharmaceutical companies in investing in the autism space has been an encouraging development, as partnerships between government, nonprofit organizations and pharmaceutical companies will be essential to filling the pipeline toward development of new pharmacotherapies for ASD.

The clinical research agenda is also very much a work in progress. The development of Autism Speaks' Autism Treatment Network (ATN) and the entry of industry into this area are both promising changes, providing potential venues and support for future trials. While in 2008, only six clinical trials for ASD were listed in ClinicalTrials.gov, currently there are 92 ASD intervention trials recruiting subjects in the U.S., including pharmacological studies to address core symptoms. Recent developments in clinical trials on the use of naturally occurring hormone oxytocin to address social impairments have yielded promising results. In an initial pilot RCT funded by Autism Speaks, researchers administered oxytocin nasal spray or a placebo to 25 children and teens twice a day for 2 months[5b]. The children who received oxytocin showed greater improvement in social behaviors compared to those who received the inactive nasal spray. The first results from a larger, follow-on NIH-funded clinical trial have demonstrated that a single spray of intranasal oxytocin can normalize brain function when performing social tasks, suggesting that oxytocin may be able to enhance social function in children[5c]. Further research on the efficacy of oxytocin therapy alone and in combination with behavioral therapy will be important areas for future study.

In addition to research on treating core symptoms, other efforts are providing insights into managing the symptoms associated with co-occurring conditions such as sleep disturbances[6-9], ADHD[10-12], and epilepsy[11-14], and gastrointestinal (GI) disturbances[15-19]. Reflecting the growing focus on co-occurring conditions, in 2012, the HRSA-funded Autism Intervention Research Network for Physical Health (AIR-P) and the ATN published empirically-validated physician guidelines for the assessment and treatment of GI, sleep, and ADHD symptoms in children with ASD[18-27]. In addition, the American Academy of Pediatrics (AAP) published guidelines for treatments of core symptoms, associated symptoms, and the use of complementary and alternative treatments[28].

Several clinical trials of behavioral interventions were completed in the last five years with some notable successes. These, early behavioral intervention trials demonstrated efficacy for significantly improving cognitive, language, and social abilities, as well as adaptive behavior, and have indicated that the improvements seen are maintained over time[29-33]. For example, the Early Start Denver Model (ESDM) has been shown to be effective in improving cognitive, language, social and adaptive behavior as well as in reducing the severity of ASD diagnosis[31-32a]. In order to facilitate translation of the ESDM model to the community, ongoing effort is focusing on alternate delivery of the intervention, such as through telehealth, community group settings, and parent-delivered approaches[32, 32b]. Another recent trial of a low intensity and brief intervention called JASPER (Joint Attention Symbolic Play Engagement and Regulation) demonstrated significant improvement compared with community treatment. The relatively lower intensity of the intervention suggests that JASPER and could be widely implemented[33].

Progress also is being made in educational intervention research. A recent comparative study of the LEAP (Learning Experiences and Alternative Program for Preschoolers and their Parents), TEACCH (Treatment and Education of Autistic and Related Communication Handicapped Children) and non-model specific special education intervention approaches showed that in high-quality special education classrooms, all approaches were effective in improving both symptom severity, as well as social, behavioral and communication skills[34]. An interesting finding is that the quality of the classroom, rather than the specific intervention method, was the most important indicator of how much the child's symptoms improved. Future work on

educational intervention approaches will be important not only to develop effective strategies, but also to learn which approaches will work best in specific subsets of children or in particular settings.

As progress on the development of interventions continues, research into biomarkers remains a high priority, and is vital to success in this field. First, identification of molecular and behavioral biomarkers of ASD will help to stratify the population, helping to direct treatments to those who are likely to benefit. For example, while as many as 50% of children will respond well to behavioral interventions, there is still a lack of good predictors of response that can help match individuals with appropriate treatments. There also still is a need for information on the effects of age of onset of treatment and dosage (low versus high intensity) of early intervention on brain and behavioral development of children with ASD.

Second, biomarkers are essential as key indicators to establish when therapies are working. Along these lines, a recent study demonstrated that early intensive behavioral intervention correlated with positive change in EEG activity that was associated with improvements in social behavior, providing the first demonstration of a physiological biomarker to indicate the effect of a behavioral treatment[35]. Additional biomarkers of treatment success are needed. Until it becomes possible to biologically measure treatment response, negative results from pharmacological and behavioral interventions will be difficult to interpret and positive results may not definitely indicate the requisite dose or duration of treatment. In addition to an improved ability to measure the initial response to treatments, there is also a need for longitudinal studies to evaluate the long-term outcomes of treatments and interventions, including measures of quality of life[35b]. In summary, autism treatment research remains a young field that shows promise, and the focus must now be on identification of consensus outcome measures (including biomarkers) that are both robust and sensitive to change.

A wide range of treatments with varying degrees of evidence to support them are widely used for ASD. The "practice to research" approach, in which information is collected from large health care systems, registries, from clinical networks such as the ATN, and through virtual, self-reporting networks such as IAN, could prove useful for assessing current interventions in real-world settings. If fully developed for ASD, the practice to research approach promises to be a fruitful strategy for collecting data on treatment effectiveness, leading more quickly to randomized trials.

New technologies, including devices to serve as social prosthetics or tools for communication assistance, are exciting opportunities for the next generation of interventions in ASD. For example, the National Science Foundation (NSF) currently funds a project to develop a robot designed to act as a social therapy tool, as many individuals with ASD interact more easily with inanimate objects. New technologies are also being used to improve communication abilities of those people with ASD who are minimally verbal. The combinations of devices, behavioral interventions, and medications will be a profound challenge for research design and regulatory approval, but may prove most useful for children and adults with complex needs.

Along with progress in developing interventions for ASD, there will continue to be a need for access to reliable information about interventions that can be accessed by providers and families considering intervention choices. Encouragingly, the past five years have seen the publication of several systematic reviews of interventions as well as the launch of new tools

such as a publicly accessible "Interventions, Treatments and Therapies for Autism" database that provides lay-friendly information about autism interventions, supported by Research Autism in the United Kingdom[36-37].

Progress towards the Aspirational Goal

Interventions that are effective for reducing both core and associated symptoms, for building adaptive skills, and for maximizing quality of life and health for people with ASD, will likely need a stronger foundation from the preceding *Strategic Plan* questions; in particular, information about the stratification of ASD (so that interventions can be tailored) and a deeper understanding of the biology of ASD (so that interventions can be effective). While in the past, serendipitous findings based on clinical observation have led to treatments for neuropsychiatric disorders without a deep understanding of the underlying biology, investment in understanding the mechanisms underlying ASD should facilitate the development of the next generation of treatments. In addition, continued improvement of behavioral, educational and technological interventions will be important. Early intervention to restore a normal developmental trajectory must remain a high priority.

There are now several medications in RCTs that are expected to be completed in 2014 or 2015. However, to-date, progress on reducing core symptoms has been most evident with early behavioral interventions. The efficacy of these treatments is powerful evidence that ASD core symptoms can be treated, even if medications or devices which might be more rapid and more accessible have yet to be developed. Looking forward, future clinical trials need to assess quality of life measures as well as reducing symptoms. In addition, effort should be made to scale up interventions that are effective in lab settings so that they may serve the broader community.

Progress has also been made in the development of treatments for several co-occurring conditions, and this continues to be an important avenue of ASD research. Associated conditions and symptoms such as epilepsy, attention deficit hyperactivity disorder (ADHD), anxiety and depression are already being treated effectively, with both medications and behavioral interventions, although more work to improve these approaches and explore the combination of medical and behavioral approaches is needed. Recent guidelines on the management of co-occurring conditions such as sleep disturbances, ADHD, and gastrointestinal (GI) issues is a clear sign of progress for families and providers[18-28], with the hope that more evidence-based guidelines will be developed in the future.

Future efforts need to address the needs of the ASD population across the lifespan. Much of the effort to develop treatments to date has focused on children, yet based on the larger proportion of life that is spent in adulthood, it is possible that the number of adults with ASD may be much larger than the number of children. Future studies must include development of treatments for individuals of all ages, including adults and adolescents, as well as children. In addition, treatments for those across the spectrum of needs must be developed including interventions for minimally verbal individuals and those with intellectual disabilities. Furthermore interventions must be tailored to individuals from diverse communities, and parents need to have access to high quality sources of information about available interventions.

While the field of ASD intervention has made important strides in the past five years, the need for a wider variety of effective intervention options to meet varying needs remains a lofty goal. Partnerships between government and private organizations and involvement of families and individuals affected by ASD in research will be essential as the community continues to work toward the aspirational goal of developing interventions that will help all people with ASD to build adaptive skills and maximize quality of life and health.

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