2012 INTERAGENCY AUTISM COORDINATING COMMITTEE STRATEGIC PLAN UPDATE: QUESTION 4 WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

WHAT IS NEW IN THIS RESEARCH AREA, AND WHAT HAVE WE LEARNED IN THE PAST 18 MONTHS?

While treatment development is still early in ASD, the past 18 months has witnessed several new findings on potentially efficacious interventions for children and adults with ASD:

Early behavioral intervention

Evidence for the benefits of early intervention continues to mount, with researchers now focusing on testing interventions for infants and toddlers, identifying "active ingredients" and dissemination of these interventions to community settings. A toddler RCT testing the efficacy of the Hanen intervention found that toddlers with poorer play skills benefited most (Carter et al., 2011). Early intensive intervention with toddlers was found to result in improvements in both social behavior and neural responses to social stimuli (Dawson et al., 2012). A 12-week, parent-delivered intervention resulted in similar child gains as standard community interventions involving more therapy hours (Rogers et al., 2012). A longitudinal follow up of a targeted joint attention intervention (Kasari et al., 2012) found that joint attention and play are important targets for enhancing language acquisition (and that these functional gains may persist over the long term). Finally, positive results of implementation of targeted interventions to community settings were reported (Kaale et al., 2012; Lawton and Kasari, 2012).

Behavioral and psychosocial interventions for school age children and adults

There is a general paucity of research on interventions with adolescents and adults, as underscored in two 2012 systematic reviews (Lounds et al., 2012; Taylor et al., 2012). These reviews noted that evidence-based approaches to support transition to adulthood and employment are particularly lacking. Although the evidence base for behavioral interventions in older children and adults is less-well developed than early intervention, new research points to a number of promising efficacious interventions. A RCT of a brief social skill intervention documented improvements in peer relationships in the classroom which persisted over time (Kasari et al., 2012). Building on earlier findings, studies showed that CBT and social skills training can be useful for decreasing anxiety in high functioning ASD and effects can be long lasting (Antshel et al., 2011; Reaven et al., 2012). Social skills training may also have positive effects on core social symptoms (DeRosier et al., 2011). One study found that mindfulness based therapy was efficacious for reducing anxiety, depression, and rumination (Spek et al., 2012).

Medications

A 2011 National Academy of Sciences report on Precision Medicine is changing the culture of treatment development (National Research Council, 2011). Noting that most common diseases may contain many rare syndromes requiring different treatments, precision medicine argues for developing treatments based on more precise diagnostics, defined by biomarkers. In an exciting example of this approach, which could serve as a model for ASD, in 2012 the FDA approved

Ivacaftor for cystic fibrosis, a breakthrough medication specifically for the 4% of cystic fibrosis with a G551D mutation.

A systematic review of medications for adolescents and young adults with ASD concluded that there is moderate evidence to support efficacy of antipsychotic medication for treating irritability, but there is also strong evidence of its adverse side effects, including sedation and weight gain (Dove at al., 2012). Scahill et al. (2012) reported that the combined effects of risperidone and parent training were more positive than medication alone for improving adaptive behavior. Hardan et al. (2012) reported potential usefulness of N-acetylcysteine, a glutamate modulator, for treating irritability. SSRIs for reducing repetitive behaviors may have age-associated or intrinsic class associated drug effects (Hollander et al., 2012; Scahill, 2012). No uniform guidance has emerged. Levetiracetam reduced interictal epileptiform discharges (IEDs) (Larsson, 2012), but the clinical significance is unclear.

Investigators are also beginning to actively link genetic tendencies with drug effects (both therapeutic as well as side effects, such as weight gain with risperidone) (Adkins et al., 2011; Correia et al., 2010). This area of research has been termed "pharmacogenomics," and its goal is to both define biomarkers of drug responsiveness within the ASD cohort, as well as identifying those who may be most prone to adverse effects.

Comment [A1]: Discussion Point: This is very early – consider leaving this part out since this has really not advanced enough.

At least twelve medication trials (Phase 1 – Phase 4) have been launched for the core domains of ASD or neurodevelopmental disorders associated with ASD, such as fragile X. A Phase 2 RCT of Arbaclofen with children and adults with fragile X (Berry-Kravis et al., 2012) showed positive effects for reducing social avoidance. At least 10 trials of the pro-social neuropeptide oxytocin are underway or recently completed in children and adolescents with ASD (www.clinicaltrials.gov).

Comment [A2]: Discussion Point: Should this be Phase 1-Phase 2 or Phase 1-Phase 4? Are there Phase 3 trials other than risperidone or other post-marketing trials? If there are some in the pipeline and not yet published, is there a way to access the results?

Treatment of co-occurring medical conditions continues to be an important area of study. A *Pediatrics* supplement (2012) based on the work of the Autism Intervention Research Network on Physical Health and the Autism Speaks Autism Treatment Network provided empirically-based physician guidelines for management of GI, sleep, and ADHD, as well as descriptive information on the prevalence and nature of a wide range of co-occurring medical conditions. Studies showed that melatonin is useful for treating insomnia in ASD (Malow et al., 2012) and that controlled-release melatonin with CBT may be useful for treating night awakening (Cortesi et al., 2012). An open label trial of donepezil was found to increase rapid eye movement (REM) sleep and decrease REM latency (Buckley et al., 2011).

Comment [A3]: Discussion Point: This is also in Question 2. Should we keep it in both places?

Other

A meta-analysis (Sowa & Meulenbroek, 2012) concluded that exercise is beneficial for social skills and motor performance for people with ASD, with individual interventions more effective than group interventions. A RCT found a movement-based yoga, dance, and music therapy program was effective for improving behavior (Rosenblatt et al., 2011). A 12-week RCT of Repetitive Transcranial Magnetic Stimulation (rTMS) in high-functioning individuals with ASD resulted in improved error-related negativity (a proxy measure of executive functioning) and improved error monitoring and correction (Sokhadze et al., 2012).

WHAT GAPS HAVE EMERGED IN THE PAST 18 MONTHS?

Although some helpful interventions for ASD have been identified, we lack a precision medicine approach: specifically, we do not have biomarkers or clinical features to indicate which interventions are helpful for whom. Trial designs need to be improved by including larger, more diverse samples (e.g., greater ethnic diversity, more non-verbal and lower functioning individuals), examination of the length and intensity of interventions, objective/physiologic measures of autonomic response or physical activity, and maintenance and generalization measures tested in authentic environments. We need to develop more sensitive outcome measures and biomarkers, so that clinical trials may identify mediators and moderators of treatment response. Thus, better characterization of biomarkers and endophenotypes may aid in the development of customized, targeted interventions.

Understanding the pathophysiology of ASD will be paramount in the quest for new treatments and delineating the mechanisms behind treatment response. The effect of co-occurring disorders on ASD (and vice versa) is unclear and needs to be better defined. We need to determine if co-occurring conditions such as anxiety and depression involve similar mechanisms in individuals with ASD as they do in typically developing individuals. It is possible that anxiety and/or affective disorders stem from core neurodevelopmental disorders; alternatively, these co-occurring conditions may actually represent reactive compensatory mechanisms in those with ASD. Treatments for co-occurring conditions may be less effective or result in paradoxical effects in some individuals with ASD.

Comment [A4]: Discussion Point: Clarify and/or need evidence to support this statement.

Alternatives to pharmacological treatments should also continue be explored, such as continued study on repetitive transcranial magnetic stimulation (rTMS) as a possible intervention. Likewise, emphasis on development of behavioral treatments should continue. As the effects of behavioral interventions become more apparent, better information regarding their "active ingredients," depth and durability are needed. The longevity of treatment effects in authentic environments must also be established.

Additionally, outcome measures that can monitor changes in brain connectivity and/or activity and correlate those changes with behavioral and social therapies should be developed. For example, more research could be conducted using electroencephalography (EEG) as a tool to measure the physiological effects of a variety of treatments, including behavioral, pharmacological, and rTMS. These measures could then be compared to concurrent changes in behavior. Likewise, standardized measures of sensory processing should be established in order to demonstrate changes in measures with occupational therapy-based interventions.

Clinically, determination of the cohorts who are most responsive to social and behavioral interventions is needed, as well as trying to better understand the mechanisms behind those benefits. As with pharmacological interventions, more data are needed for behavioral treatments regarding for whom treatments work best and the mechanisms behind those benefits.
A number of cognitive, educational and computer-based programs are used to remediate learning deficits in ASD individuals in an effort to help them meet their cognitive and learning potential. These should be compared in well-characterized ASD cohorts to determine which are most

effective. Additionally, effectiveness studies for relatively inexpensive community-based interventions (e.g., exercise, yoga, acupuncture, mindfulness) should also be conducted.

Interventions that are commonly used yet have little evidence need to be rigorously evaluated so they can be disregarded if found ineffective. Self-advocates have raised concerns about the potential iatrogenic effects of interventions. This applies not only to pharmacological treatments, including the two medications currently FDA-approved to treat irritability, but to behavioral interventions. While many behavioral interventions report success upon the decrease of a targeted behavior, some have raised a concern about the net, not gross, effects of a targeted intervention, including the unintentional development of alternate problem behaviors and effects on stress levels, unique talents, and quality of life. Measures studying these effects need to be developed. An important goal for any intervention is to help individuals with ASD understand and utilize their strengths, and help them channel their interests towards useful activities. An understudied phenomenon is that being placed in a group of autistic peers appears to increase friendships amongst people with ASD, regardless of the particular group purpose or intervention style.

Comment [A5]: Discussion Point: This is based on unpublished research.

Word count: 1602

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