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 TWO YEARS?

While treatment development for ASD is still in its early stages, several new findings on potentially efficacious interventions for children and adults with ASD have arisen during the past two years:

Early Behavioral Interventions

Evidence for the benefits of early behavioral intervention continues to mount, with researchers now focusing on testing interventions for infants and toddlers, identifying the most effective aspects of treatments and disseminating these interventions in community settings. , Positive results of implementation of targeted interventions in community settings have recently been reported (Kaale, Smith & Sponheim, 2012; Lawton & Kasari, 2012).

A randomized clinical trial (RCT) in toddlers with ASD, testing the efficacy of Hanen's "More Than Words," a parent-implemented intervention, found that toddlers with poorer play skills benefited most (Carter et al., 2011). Furthermore, a longitudinal follow up of a targeted, joint attention intervention (Kasari et al., 2012b) found that joint attention and play are important targets for interventions aimed at enhancing language acquisition (and that these functional gains may persist over the long-term).

Early intensive intervention using the Early Start Denver Model (ESDM) with toddlers was found to result in improvements in both social behavior and neural responses to social stimuli (Dawson et al., 2012). This was the first study to demonstrate that behavioral interventions can result in changes in electrophysiological brain activity (specifically, event related potentials (ERPs) and electroencephalography (EEG) spectral power in response to social stimuli), and that this biological marker correlated with positive changes in behavior. In a different RCT, children who received a 12-week, parent-delivered ESDM intervention were compared to a control group of children receiving typical community interventions over the same period of time (although note that the latter group received more intervention hours per week) (Rogers et al., 2012). Both groups of children showed developmental gains and reduced core autism symptoms. The degree of improvement across both community and ESDM groups was higher in children that received more hours of intervention, and younger children (14 months) made more developmental gains than older children (24 months).

Behavioral and Psychosocial Interventions for School Age Children and Adults

There is a general paucity of research on interventions for adolescents and adults, as underscored by one systematic review this year (Taylor et al., 2012). This review 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 interventions, new research points to a number of promising efficacious interventions. An RCT of a brief social skills intervention, documented improvements in peer relationships in the classroom which persisted over time (Kasari et al., 2012a). In another pair of studies that built on earlier findings, cognitive behavioral therapy (CBT) and social skills training were useful for decreasing anxiety in high functioning individuals with ASD, and the 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). Additionally, one RCT that addressed common psychiatric concerns in ASD found that mindfulness-based therapy was efficacious for reducing anxiety, depression, and rumination in adults (Spek, van Ham & Nyklíček , 2012).

Medications

To date, the only medications approved by the Food and Drug Administration (FDA) for the treatment of any aspect of ASD are aripiprazole and risperidone, both for the treatment of irritability associated with ASD. A recent meta-analysis (which contrasts and combines results from different studies to identify patterns among the results) of these medications for adolescents and children with ASD concluded that, while these drugs are effective in the treatment of behavioral disturbances, there are frequently adverse side effects including sedation, involuntary muscle spasms, and weight gain (Cohen 2013). In a study combining treatment and intervention, the combined effects of risperidone and parent training were more positive than medication alone for improving adaptive behavior (Scahill et al., 2012a). Another group of researchers reported potential usefulness of N-acetylcysteine, a glutamate modulator, for treating irritability (Hardan et al., 2012).

Clinical trials for selective serotonin reuptake inhibitors (SSRIs) for reducing repetitive behaviors have produced conflicting results for adults and children, indicating that there may be age-associated drug effects or effects intrinsic to this particular class of drugs (Hollander et al., 2012; Scahill et al., 2012b). No uniform guidance has yet emerged from these studies.

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

Treatment of co-occurring medical conditions continues to be an important area of study. A *Pediatrics* supplement (Perrin & Coury, ed., 2012) based on the work of the Autism Intervention Research Network on Physical Health (AIR-P) and the Autism Speaks Autism Treatment Network (ATN) provided empirically-based physician guidelines for the management of gastrointestinal (GI) issues, sleep, and attention deficit hyperactivity disorder (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 in children with ASD (Buckley et al., 2011).

Epilepsy—which commonly co-occurs with ASD—and interictal epileptiform discharges (patterns of electrical activity which resemble those during seizures but are present between seizures) are also associated with sleep disruption. Recently, the antiepileptic drug levetiracetam was shown to reduce nocturnal epileptiform activity (which is present in many individuals that lack a clinical diagnosis of epilepsy) during non-rapid eye movement (REM) sleep (Larsson, 2012).

In the broader context of biomedical research, 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 the future, identification of biomarkers for autism could advance the autism treatment field as well.

Other Treatments and Interventions

A number of other treatments and interventions for ASD have been studied during the past 18 months. For example, a meta-analysis, concluded that exercise is beneficial for social skills and motor performance for people with ASD, with individual interventions more effective than group interventions (Sowa & Meulenbroek, 2012). Additionally, an RCT found that a movement-based yoga, dance, and music therapy program was effective for improving behavior (Rosenblatt et al., 2011). Finally, 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 TWO YEARS?

Although some helpful interventions for ASD have been identified, a precision medicine approach is lacking. Specifically, no biomarkers or clinical features have been identified 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 individuals with more severe disability challenges, such as individuals with limited or no verbal communication), examining the length and intensity of interventions, developing objective/physiologic measures of autonomic response or physical activity, and conducting maintenance and generalization measures tested in authentic environments. More sensitive outcome measures and biomarkers need to be developed 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.

Investigators are also beginning to actively link genetic makeup 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 among people with ASD, as well as to identify those who may be most prone to adverse effects.

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 conditions on ASD (and vice versa) is unclear and needs to be better defined. Research needs to be done to determine if co-occurring conditions such as anxiety, depression, gastrointestinal issues, epilepsy, or atypical immune response involve similar mechanisms in individuals with ASD as they do in non-autistic individuals. It is possible that anxiety and/or affective disorders in individuals with ASD stem from core aspects of atypical neurodevelopment in ASD; alternatively, these co-occurring conditions may actually represent reactive compensatory mechanisms in those with ASD. It is also important to understand whether treatments for co-occurring conditions have similar effects in individuals with ASD and non-autistic individuals.

Alternatives to pharmacological treatments should also continue be explored, for example the use of repetitive transcranial magnetic stimulation (rTMS) as a possible intervention should continue to be studied. Likewise, emphasis on development of behavioral treatments should continue. As the effects of behavioral interventions become more apparent, better information regarding the most critical components of treatment are needed. The effectiveness and longevity of treatment effects in real world settings 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 magnetic resonance imaging (MRI) or 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. This approach has already been used successfully to study the effect of behavioral interventions using EEG (see study described above, Dawson et al., 2012) and functional MRI (Voos et al., 2012). Likewise, standardized measures of sensory processing should be established in order to demonstrate changes in measures with occupational therapy-based interventions.

Clinically, determination of which individuals are most likely to be responsive to particular social and behavioral interventions is needed, as well as efforts to better understand the mechanisms behind efficacy in those individuals. In addition, there is a need for further research on the many cognitive, educational and computer-based programs used to remediate learning deficits in individuals with ASD to determine which are most effective. These should be compared in well-characterized ASD cohorts. Better understanding of which interventions are likely to be effective for different individuals will help individuals to select the interventions that will best help them meet their cognitive and learning potential. Effectiveness studies for relatively inexpensive community-based interventions (e.g., exercise, yoga, acupuncture, mindfulness) should also be conducted.

Some interventions are widely used despite a limited evidence base. These include complementary and alternative treatment approaches, among others. There is a need for more research on these interventions so that consumers can make informed choices about their use. The needed research includes studies to identify potential principles and mechanisms of action, and to evaluate safety and efficacy. In addition, research that explores the potential treatment implications of novel biological findings, such as differences in immune functioning in individuals with autism, is needed.

While many interventions (pharmacological, behavioral, and otherwise) successfully change targeted behaviors or symptoms, there is a need to measure the global, not merely the specific, effects of all interventions. These effects may include unintentional development of alternate problem behaviors, as well as effects on stress levels, unique talents, and overall life satisfaction (including satisfaction with social and peer groups). When possible, studies should include self-report measures from people with autism who serve as study participants. For example, data from self-report measures might help us understand if the benefits of interventions targeting "harmless" autistic behaviors (e.g., "stimming") outweigh the risk of provoking anxiety or confusion. A worthy goal for any intervention is to help individuals with ASD understand and utilize their strengths. All research involving human participants must be conducted in accordance with high ethical standards, minimizing harms and risks and maximizing benefits; respecting human dignity, privacy, and autonomy; taking special precautions with vulnerable populations; and striving to distribute the benefits and burdens of research fairly. The described research will play an important role in distinguishing effective interventions from ineffective ones, and in identifying risks and benefits that should be taken into consideration before using these interventions.

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