Research in Autism Spectrum Disorders 5 (2011) 230–236

Contents lists available at ScienceDirect

Research in Autism Spectrum Disorders

Journal homepage: http://ees.elsevier.com/RASD/default.asp

Psychotropic drug efficacy and side effects for persons with autism spectrum disorders

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ARTICLE INFO

Article history:
Received 2 March 2010
Accepted 5 April 2010

Keywords:
Autism
Psychotropic drugs
Side effects

ABSTRACT

Pharmacotherapy is a frequently employed treatment option in the area of autism spectrum disorders (ASD). A considerable literature base has developed indicating when these medications should or could be administered. However, research on the potential side effects and cost benefit analysis of these treatments is not well understood at this time. The purpose of this review is to assess current prescription practices, to determine what is needed with respect to better understanding the cost and benefits of these prescription practices, and notions about future trends in research to better aid in our understanding of psychotropic drug side effects. Future research of this sort should further establish best practices with respect to pharmacotherapy and ASD.

Autism spectrum disorders (ASD) are a set of five neurodevelopmental disorders with common core features (Matson & Boisjoli, 2007; Matson, 2007a, 2007b; Matson et al., 1996). Communication, rituals and stereotypies, and social skills constitute the primary defining characteristics, although strengths and weaknesses in these symptoms may vary considerably across individuals (Chiang, 2008; Matson & Wilkins, 2009; Matson, Carlisle, & Bamburg, 1998; Matson, Smiroldo, & Bamburg, 1998). These problems are compounded by high rates of co-occurring disorders such as intellectual disabilities (ID; Matson, Dempsey, LoVullo, & Wilkins, 2008), challenging behaviors (Appelgate, Matson, & Cherry, 1999; Dawson, Matson, & Cherry, 1998; Hartley, Sikora, & McCoy, 2008; Matson & Nebel-Schwalm, 2007a), comorbid psychopathology (Matson & Bamburg, 1998; Matson & Nebel-Schwalm, 2007b) and feeding problems (Matson, Fodstad, & Boisjoli, 2008). Furthermore, ID occurs in approximately 70% of ASD cases and ID also co-occurs at high rates with psychopathology (Matson & Shoemaker, 2009; Matson & Smiroldo, 1997). As a result, while children and adults with developmental disabilities constitute a small percentage of the overall population, they require an inordinate amount of time, resources, and expertise for their treatments (Calles, 2008). These problems are compounded by ever increasing rates of ASD (Mattila et al., 2008; Shattuck, 2006), and the fact that challenging behaviors (CB) occur frequently in persons with ASD further exacerbates the equation (Cohen et al., in press; Farmer & Aman, 2009).

Psychotropic drug use for children and individuals with developmental disabilities has been expanding rapidly over the last three decades (Provenzano & Mantia, 2008). Provenzano and Mantia (2008) point out that the use of such drugs is indeed controversial. While core symptoms of ASD do not appear to respond to antipsychotic drugs, medication use continues to increase. Stigler and McDougle (2008) claim that irritability (i.e., defined as aggression, self-injury, and tantrums), should be treated with atypical antipsychotics as the first-line of pharmacology. However, the notion that irritability is the cause of CB is at best questionable. Irritability is further defined in terms of subfactor scores from the Aberrant Behavior Checklist, which was never designed for this purpose (Aman & Singh, 1994; Scott & Dhillon, 2007). Finally, many of these same authors refer

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doi:10.1016/j.rasd.2010.04.004

to treatment targets as challenging behaviors, as opposed to irritability in other studies (McCracken et al., 2002; Scott & Dhillon, 2007). These changing, multiple definitions add further confusion to what is actually being treated. Furthermore, Armstrong (2008) outlined the prescription practices for prescribing psychotropic medications and also lists repetitive behaviors, perseverations, obsessions, compulsions, stereotypies, sleep disturbance, mood lability, anxiety, hyperactivity, inattention, or "other disruptive behaviors" as treatment targets. Finally, Stachnik and Nunn-Thompson (2007) recommend "atypical" antipsychotics to treat symptoms which are "similar" to negative symptoms in schizophrenia, despite the lack of clinical/research data to support similar neuropathways. It is hard to imagine any child with a developmental disability who does not have one or several of these behaviors. Thus, the rationales for psychotropic drug administration appear to be all inclusive and almost endless.

Other issues in evaluating drug efficiency are also evident. First, there is the issue of whether a distinction between typical and atypical antipsychotics is defensible (Tyrer & Kendall, 2009). Second, the assumption that antipsychotic medication is effective for CB has a limited evidence base (Oliver-Africano et al., 2010) and they are a very expensive mode of treatment (Tyrer et al., 2009). Furthermore, some investigators have found typical antipsychotics to be no more effective than a placebo for treating CB in individuals diagnosed with developmental disabilities (Tyrer et al., 2009). Despite these data, antipsychotic drugs, particularly the atypical antipsychotics, are recommended for exactly these target behaviors (Calles, 2008). Also, these drugs have been used in very young children. For example Nagaraj, Singhi, and Malhi (2006) describe the use of Risperidone in children as young as two years of age who were believed to have an ASD. We will review these prescription practices in some detail, followed by an analysis of the available data on side effects.

1. Prescription practices

Pharmacotherapy has been actively pursued since the 1960s (Stigler & McDougle, 2008). Approximately half of individuals diagnosed with high functioning ASD are on at least one psychotropic: antidepressants, stimulants, antipsychotics, or anti-epileptics (Santosh & Baird, 2001). Cautionary points have been made, such as using the minimal effective dose (Santosh & Suren, 2008). Without systematic evaluation of side effects, it is difficult to establish these parameters. However, this is rarely done, as open label and case study reports are often the medium of investigation (Fido & Al-Saad, 2008) and methods of establishing effects on target behaviors are often loosely defined (e.g., favorable response; Durukan, Tufan, & Türkbay, 2009). There also appears to be a general view among many medical professionals that these drugs are safe and effective (Findling, 2005; McDougle, Stigler, Erickson, & Posey, 2006; Myers, 2007; Parikh, Kolevzon & Hollander, 2008; Poustka & Poustka, 2007; Stachnik & Nunn-Thompson, 2007).

2. Determining effectiveness

However, another factor pertains to how "effective" is defined. Armand-Branger, Poisson, Gaudoneix-Taïeb, and Ramos (2009) list obtaining behavioral or antipsychotic sedation as a treatment objective. They also point out that high doses are needed to meet this objective and they note that prescription practices are similar across developmentally disabled groups (ASD versus multi-handicapped). Malone and Waheed (2009) on the other hand suggest the use of antipsychotics to reduce ASD core symptoms, despite the fact that most investigators insinuate that they do not produce a positive effect on core behaviors of ASD.

An often repeated point is that when behavioral interventions are not fully effective, psychotropic drugs should be considered. However, who defines, "not fully effective"? For example, how long should the intervention be presented, what specific applied behavior analysis methods are employed and how is that determined, what type of education should the trainer posses, and so on. To our knowledge, no guidelines have been developed to address any of these issues. Finally, as noted, Nagaraj et al. (2006) describe the use of Risperidone to treat children with ASD who were as young as two years of age. We do not consider it credible to determine if behavioral treatments could be established as "ineffective" as such an early age. Years of intervention would be needed to determine effectiveness of applied behavior analysis. More likely, and as we have seen over and over again in clinical practices, these very powerful medications are often prescribed where no behavioral interventions or attempts to seek behavioral interventions have occurred. Given this situation, clear cut triggers for such decisions do not exist.

3. Rationale to treat

One rationale for pharmacology is that behaviorally based treatments may be too limited for timely access. This latter point is undoubtedly true, but does not appear to be a particularly compelling reason for psychotropic medication use for CB in individuals diagnosed with ASD. The lack of availability of one method does not prove the effectiveness of another. Certainly, one of many other educational methods might also be considered as an interim treatment. Considering how to increase the availability of the most effective interventions should be another strategy.

Researchers have found no strong evidence that ASD has dopamine involvement, which is the primary mechanism for the action of antipsychotic medications (Mohammadi & Akhondzadeh, 2007). Therefore, a mechanism for effectiveness is not evident. Having said that, the use of antipsychotic drugs for children and adults diagnosed with ASD continues to increase (Witwer & Lecavalier, 2005). So, why are individuals with ASD being treated with more and more psychotropic medication?