|  |
| --- |
| **Summary of key trials into the use of psychotropic agents in treating core or associated features of ASD** |
| **Pharmacological agent** | **Dose**  | **Study design** | **Sample size (n=)** | **Duration** | **Outcome(s)** | **Reference** |
| Fluoxetine | 9.9 **±** 4.35 mg/day | Randomized, double-blind placebo-controlled crossover study | 45 | Two randomized 8-week fluoxetine and placebo phases separated by a 4-week washout phase | Liquid fluoxetine in low doses is more effective than placebo in the treatment of repetitive behaviours in childhood ASD | (Hollander et al., 2005) |
| 0.15-0.5mg/kg/day | Open label, retrospective study | 129 | Mean of 32 to 36 months | Significant improvements irritability and repetitive behaviours for those taking fluoxetine | (DeLong et al., 2002) |
| 11.8 mg/day | Randomized, double-blind placebo-controlled trial | 158 | 14 weeks | No significant differences were noted on the Children's Yale-Brown Obsessive Compulsive Scale and similar rates of adverse effects | (Herscu et al., 2020) |
| Mean dose not specified. Flexible titration schedule up to 20 mg/d (<40 kg) or 30 mg/d (≥40 kg) | Multicentre, randomised, placebo-controlled clinical trial | 146 | 16 weeks | Fluoxetine lead to lower scores for obsessive-compulsive behaviours at 16 weeks but with concerns over high dropout rate, confounding factors and baseline imbalances | (Reddihough et al., 2019) |
| Citalopram | 16.5 **±** 6.1 mg/day | Multicentre, randomized controlled trial, double-blind, placebo-controlled | 149 | 12 weeks | No significant difference on the Clinical Global Impressions or Children's Yale-Brown Obsessive Compulsive Scales but citalopram was significantly more likely to be associated with adverse events | (King et al., 2009) |
| Escitalopam | Forced titration dosing regimen. Overall mean dose not specified | Open label design, genotype blind, prospective pharmacogenetic study | 58 | 10 weeks | Group of subjects with associated with the lowest platelet 5-HT uptake from had the smallest reduction in ABC-Irritability scores | (Owley et al., 2010) |
| 11.1 ± 6.5 mg/day (forced titration dosing regimen) | Open-label design | 28 | 10 weeks | 25% of the subjects responded at a dose less than 10 mg and did not tolerate the 10 mg dose, and an additional 36% responded at a dose greater than or equal to 10 mg | (Owley et al., 2005) |
| Fluvoxamine | 276.7 ± 41.7 mg/day | Randomised, double-blind, placebo-controlled trial | 30 | 12 weeks | Fluvoxamine is more effective than placebo in the short-term treatment of the symptoms of ASD in adults | (McDougle et al., 1996) |
| 1.5 mg/kg/day | Prospective, open-label trial | 18 | 10 weeks | No response for the group. Eight subjects (including all four females) were considered at least partial responders in intent-to-treat analyses | (Martin et al., 2003) |
| Risperidone | Low-dose: 0.125 mg/day (<45 kg) or 0.175 mg/day (>45 kg). High-dose: 1.25 mg/day (<45 kg) or 1.75 mg/day (>45 kg) | Randomised, double-blind, placebo-controlled study | 96 | 6 weeks | Greater reduction in ABC-irritability, Clinical Global Impressions-Improvement Scale and Children's Yale-Brown Obsessive Compulsive Scale in the high-dose but not low-dose group. Somnolence, sedation and increased appetite occurred more frequently in high-versus low-dose groups | (Kent et al., 2013) |
| RCT: 1.8 ± 0.7 mg/dayOpen-label: 2.0 ± 1.2 mg/day | Double-blind, placebo-controlled trial and 16-week open-label continuation study | RCT: 101Open-label study: 63 | RCT: 8 weeksOpen-label study: 16 weeks | Risperidone led to significant improvements in RRBs but did not significantly change their deficit in social interaction and communication | (McDougle et al., 2005) |
| 1 mg/day | Randomised, double-blind, placebo-controlled trial | 40 | Six months | Risperidone improved global functioning and social responsiveness while reducing hyperactivity and aggression in children with ASD and was well tolerated | (Nagaraj et al., 2006) |
| 1.37 ± 0.7 mg/day | Randomised, double-blind, placebo-controlled trial | 55 | 8 weeks | Risperidone treatment was well tolerated and significantly improved behavioural problems associated with ASD | (Pandina et al., 2007) |
| 1.8 ± 0.7 mg/day | Multisite, randomized, double-blind trial, placebo controlled | 101 | 8 weeks | Risperidone was effective and well tolerated for the treatment of tantrums, aggression, or self-injurious behaviour in children with autistic disorder | (McCracken et al., 2002) |
| Aripiprazole | 2.5-15 mg/day | Meta-analysis | 316 | 8 weeks | Aripiprazole can be effective in treating some behavioural aspects of ASD in children including less irritability, hyperactivity, and stereotypies. Notable side effects must be considered such as weight gain, sedation, drooling, and tremor | (Ching and Pringsheim, 2012) |
| Target dosage of 5, 10, or 15 mg/day (maximum dosage: 15 mg/day). Mean doses not specified | Double-blind, randomized, placebo-controlled, parallel-group study | 98 | 8 weeks | Aripiprazole was efficacious in children and adolescents with irritability associated with ASD and was generally safe and well tolerated | (Owen et al., 2009) |
| 5 (n=53), 10 (n=59), or 15 (n=54) mg/day. No mean dose specified | Double-blind, randomized, placebo-controlled, parallel-group study | 218 | 8 weeks | Aripiprazole was efficacious and generally safe and well tolerated in the treatment of children and adolescents with irritability associated with ASD | (Marcus et al., 2009) |
| 2-15 mg/day | Open-label, flexible-dose study | 330 | 52 weeks | Aripiprazole reduced symptoms of irritability associated with ASD in paediatric subjects ages 6-17 years | (Marcus et al., 2011) |
| 2–15 mg/day | Multicentre, double-blind, randomised, placebo-controlled, relapse-prevention trial | 85 | Up to 42 weeks | No statistically significant difference between aripiprazole and placebo in time to relapse during maintenance therapy | (Findling et al., 2014) |
| 2–15 mg/day | Systematic review & meta-analysis | 3 x RCTs (n=401) | Up to 42 weeks | Aripiprazole can be effective as a short‐term medication intervention for some behavioural aspects of ASD in children and adolescents. Relapse rates did not differ between aripiprazole versus placebo | (Hirsch and Pringsheim, 2016) |
| Risperidone & aripiprazole | Risperidone: 1.2 and 1.8 mgAripiprazole: 2–15 mg/day | A systematic review and meta-analysis | 1673 | 4-8 weeks (depending on the included study) | Risperidone and aripiprazole were found to be the most effective in reducing irritability and aggression, but with a risk of sedation, extrapyramidal sides effects, and weight gain | (Fung et al., 2016) |
| Risperidone: 1.12 mg/dayAripiprazole: 5.5mg/day | Randomized double blind clinical trial | 59 | 2 months | Aripiprazole as well as risperidone lowered ABC scores. The rates of adverse effects were not significantly different between the two groups | (Ghanizadeh et al., 2014) |
| Risperidone & haloperidol | Haloperidol: 2.6 ± 1.3 mg/dayRisperidone: 2.6 ± 0.8 mg/day | Randomized, controlled, double-blind trial | 30 | 12 weeks | Compared to haloperidol, risperidone led to a significantly greater reduction in the ABC checklist but also a greater increase of prolactin in the risperidone group | (Miral et al., 2008) |
| Olanzapine | 7.5-12.5 mg/d | Randomised, double-blind placebo-controlled pilot study | 11 | 8 weeks | 50% of those on olanzapine much or very much improved in global functioning vs. 20% on placebo | (Hollander et al., 2006b) |
| Quetiapine | 100 to 350 mg/day | Open label trial | 6 | 16 weeks | Quetiapine was poorly tolerated and associated with serious side effects in children and adolescents with ASD | (Martin et al., 1999) |
| 300-750mg/day (mean dose not specified) | Open label trial | 9 | 12 weeks | Only 2 patients met a priori criteria for response on the Clinical Global Impressions-Improvement Scale | (Findling et al., 2004) |
| Paliperidone | 7.1 mg/day | Open label trial | 25 | 8 weeks | Paliperidone treatment was associated with significant improvement in irritability and was generally well tolerated | (Stigler et al., 2012) |
| Ziprasidone | 98.3 **±** 40.4 mg/day | Open label trial | 12 | 6 weeks | 75% of patients on ziprasidone were treatment responders. Ziprasidone was weight neutral, and the QTc increased by a mean of 14.7 msec | (Malone et al., 2007) |
| Lurasidone | 20 mg/day vs. 60mg/day vs. placebo | Randomised, double-blind placebo-controlled trial | 150 | 6 weeks | 20 and 60 mg/day of lurasidone were not efficacious compared to placebo for the short-term treatment of irritability in children and adolescents with ASD | (Loebel et al., 2016) |
| Haloperidol | 0.844 mg/day (range 0.25-4 mg/day | Randomised, double-blind and placebo-controlled, crossover trial | 45 | 4 weeks | Haloperidol led to improved behavioural over four weeks without notable side effects | (Anderson et al., 1989) |
| Sodium valproate | 822.92 **±** 326.21 mg/day(range: 500–1500 mg/day) | Randomised, double-blind placebo-controlled trial | 13 | 8 weeks | There was a significant group difference on improvement in repetitive behaviours as measured by the Children's Yale-Brown Obsessive Compulsive Scale | (Hollander et al., 2006a) |
|  | 25.5 **±** 8.58 mg/kg vsnon-responders 22.7 **±** 0.83 mg/kg. No mean total dose across groups was specified | Randomised, double-blind, placebo-controlled trial | 55 | 12 weeks | A significant improvement was noted on the ABC-Irritability subscale. There was a trend for responders to have higher valproate blood levels compared with non-responders | (Hollander et al., 2010) |
| Lamotrigine | 5.0 mg/kg per day | Randomised, double-blind, placebo-controlled trial | 28 | 18 weeks | No significant difference in improvements between lamotrigine or placebo groups | (Belsito et al., 2001) |
| Levetiracetam | 20-30 mg/kg/d | Double-blind placebo-controlled study | 20 | 10 weeks | Levetiracetam does not improve behavioural disturbances of ASD. | (Wasserman et al., 2006) |

Abbreviations: 5-HT: 5-hydroxytryptamine; ABC: Abberant Behaviour Checklist; ASD: autism spectrum disorder; ADHD: kg: kilograms; mg: milligrams; RRB: restricted and repetitive behaviour

**References**

ANDERSON, L. T., CAMPBELL, M., ADAMS, P., SMALL, A. M., PERRY, R. & SHELL, J. 1989. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. *J Autism Dev Disord,* 19**,** 227-39.

BELSITO, K. M., LAW, P. A., KIRK, K. S., LANDA, R. J. & ZIMMERMAN, A. W. 2001. Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. *J Autism Dev Disord,* 31**,** 175-81.

CHING, H. & PRINGSHEIM, T. 2012. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev***,** Cd009043.

DELONG, G. R., RITCH, C. R. & BURCH, S. 2002. Fluoxetine response in children with autistic spectrum disorders: correlation with familial major affective disorder and intellectual achievement. *Developmental medicine and child neurology,* 44**,** 652-659.

FINDLING, R. L., MANKOSKI, R., TIMKO, K., LEARS, K., MCCARTNEY, T., MCQUADE, R. D., EUDICONE, J. M., AMATNIEK, J., MARCUS, R. N. & SHEEHAN, J. J. 2014. A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *J Clin Psychiatry,* 75**,** 22-30.

FINDLING, R. L., MCNAMARA, N. K., GRACIOUS, B. L., O'RIORDAN, M. A., REED, M. D., DEMETER, C. & BLUMER, J. L. 2004. Quetiapine in Nine Youths with Autistic Disorder. *Journal of Child and Adolescent Psychopharmacology,* 14**,** 287-294.

FUNG, L. K., MAHAJAN, R., NOZZOLILLO, A., BERNAL, P., KRASNER, A., JO, B., COURY, D., WHITAKER, A., VEENSTRA-VANDERWEELE, J. & HARDAN, A. Y. 2016. Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis. *Pediatrics,* 137**,** S124.

GHANIZADEH, A., SAHRAEIZADEH, A. & BERK, M. 2014. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev,* 45**,** 185-92.

HERSCU, P., HANDEN, B. L., ARNOLD, L. E., SNAPE, M. F., BREGMAN, J. D., GINSBERG, L., HENDREN, R., KOLEVZON, A., MELMED, R., MINTZ, M., MINSHEW, N., SIKICH, L., ATTALLA, A., KING, B., OWLEY, T., CHILDRESS, A., CHUGANI, H., FRAZIER, J., CARTWRIGHT, C. & MURPHY, T. 2020. The SOFIA Study: Negative Multi-center Study of Low Dose Fluoxetine on Repetitive Behaviors in Children and Adolescents with Autistic Disorder. *J Autism Dev Disord,* 50**,** 3233-3244.

HIRSCH, L. E. & PRINGSHEIM, T. 2016. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database of Systematic Reviews*.

HOLLANDER, E., CHAPLIN, W., SOORYA, L., WASSERMAN, S., NOVOTNY, S., RUSOFF, J., FEIRSEN, N., PEPA, L. & ANAGNOSTOU, E. 2010. Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology,* 35**,** 990-8.

HOLLANDER, E., PHILLIPS, A., CHAPLIN, W., ZAGURSKY, K., NOVOTNY, S., WASSERMAN, S. & IYENGAR, R. 2005. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. *Neuropsychopharmacology,* 30**,** 582-9.

HOLLANDER, E., SOORYA, L., WASSERMAN, S., ESPOSITO, K., CHAPLIN, W. & ANAGNOSTOU, E. 2006a. Divalproex sodium vs. placebo in the treatment of repetitive behaviours in autism spectrum disorder. *Int J Neuropsychopharmacol,* 9**,** 209-13.

HOLLANDER, E., WASSERMAN, S., SWANSON, E. N., CHAPLIN, W., SCHAPIRO, M. L., ZAGURSKY, K. & NOVOTNY, S. 2006b. ADouble-Blind Placebo-Controlled Pilot Study of Olanzapine in Childhood/Adolescent Pervasive Developmental Disorder. *Journal of Child and Adolescent Psychopharmacology,* 16**,** 541-548.

KENT, J. M., KUSHNER, S., NING, X., KARCHER, K., NESS, S., AMAN, M., SINGH, J. & HOUGH, D. 2013. Risperidone Dosing in Children and Adolescents with Autistic Disorder: A Double-Blind, Placebo-Controlled Study. *Journal of Autism and Developmental Disorders,* 43**,** 1773-1783.

KING, B. H., HOLLANDER, E., SIKICH, L., MCCRACKEN, J. T., SCAHILL, L., BREGMAN, J. D., DONNELLY, C. L., ANAGNOSTOU, E., DUKES, K., SULLIVAN, L., HIRTZ, D., WAGNER, A. & RITZ, L. 2009. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. *Arch Gen Psychiatry,* 66**,** 583-90.

LOEBEL, A., BRAMS, M., GOLDMAN, R. S., SILVA, R., HERNANDEZ, D., DENG, L., MANKOSKI, R. & FINDLING, R. L. 2016. Lurasidone for the Treatment of Irritability Associated with Autistic Disorder. *J Autism Dev Disord,* 46**,** 1153-63.

MALONE, R. P., DELANEY, M. A., HYMAN, S. B. & CATER, J. R. 2007. Ziprasidone in adolescents with autism: an open-label pilot study. *J Child Adolesc Psychopharmacol,* 17**,** 779-90.

MARCUS, R. N., OWEN, R., KAMEN, L., MANOS, G., MCQUADE, R. D., CARSON, W. H. & AMAN, M. G. 2009. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry,* 48**,** 1110-1119.

MARCUS, R. N., OWEN, R., MANOS, G., MANKOSKI, R., KAMEN, L., MCQUADE, R. D., CARSON, W. H., COREY-LISLE, P. K. & AMAN, M. G. 2011. Aripiprazole in the treatment of irritability in pediatric patients (aged 6-17 years) with autistic disorder: results from a 52-week, open-label study. *J Child Adolesc Psychopharmacol,* 21**,** 229-36.

MARTIN, A., KOENIG, K., ANDERSON, G. M. & SCAHILL, L. 2003. Low-dose fluvoxamine treatment of children and adolescents with pervasive developmental disorders: a prospective, open-label study. *J Autism Dev Disord,* 33**,** 77-85.

MARTIN, A., KOENIG, K., SCAHILL, L. & BREGMAN, J. 1999. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. *J Child Adolesc Psychopharmacol,* 9**,** 99-107.

MCCRACKEN, J. T., MCGOUGH, J., SHAH, B., CRONIN, P., HONG, D., AMAN, M. G., ARNOLD, L. E., LINDSAY, R., NASH, P., HOLLWAY, J., MCDOUGLE, C. J., POSEY, D., SWIEZY, N., KOHN, A., SCAHILL, L., MARTIN, A., KOENIG, K., VOLKMAR, F., CARROLL, D., LANCOR, A., TIERNEY, E., GHUMAN, J., GONZALEZ, N. M., GRADOS, M., VITIELLO, B., RITZ, L., DAVIES, M., ROBINSON, J. & MCMAHON, D. 2002. Risperidone in children with autism and serious behavioral problems. *N Engl J Med,* 347**,** 314-21.

MCDOUGLE, C. J., NAYLOR, S. T., COHEN, D. J., VOLKMAR, F. R., HENINGER, G. R. & PRICE, L. H. 1996. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Arch Gen Psychiatry,* 53**,** 1001-8.

MCDOUGLE, C. J., SCAHILL, L., AMAN, M. G., MCCRACKEN, J. T., TIERNEY, E., DAVIES, M., ARNOLD, L. E., POSEY, D. J., MARTIN, A., GHUMAN, J. K., SHAH, B., CHUANG, S. Z., SWIEZY, N. B., GONZALEZ, N. M., HOLLWAY, J., KOENIG, K., MCGOUGH, J. J., RITZ, L. & VITIELLO, B. 2005. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. *Am J Psychiatry,* 162**,** 1142-8.

MIRAL, S., GENCER, O., INAL-EMIROGLU, F. N., BAYKARA, B., BAYKARA, A. & DIRIK, E. 2008. Risperidone versus haloperidol in children and adolescents with AD : a randomized, controlled, double-blind trial. *Eur Child Adolesc Psychiatry,* 17**,** 1-8.

NAGARAJ, R., SINGHI, P. & MALHI, P. 2006. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol,* 21**,** 450-5.

OWEN, R., SIKICH, L., MARCUS, R. N., COREY-LISLE, P., MANOS, G., MCQUADE, R. D., CARSON, W. H. & FINDLING, R. L. 2009. Aripiprazole in the Treatment of Irritability in Children and Adolescents With Autistic Disorder. *Pediatrics,* 124**,** 1533.

OWLEY, T., BRUNE, C. W., SALT, J., WALTON, L., GUTER, S., AYUYAO, N., GIBBONS, R. D., LEVENTHAL, B. L. & COOK, E. H. 2010. A pharmacogenetic study of escitalopram in autism spectrum disorders. *Autism Res,* 3**,** 1-7.

OWLEY, T., WALTON, L., SALT, J., GUTER, S. J., JR., WINNEGA, M., LEVENTHAL, B. L. & COOK, E. H., JR. 2005. An open-label trial of escitalopram in pervasive developmental disorders. *J Am Acad Child Adolesc Psychiatry,* 44**,** 343-8.

PANDINA, G. J., BOSSIE, C. A., YOUSSEF, E., ZHU, Y. & DUNBAR, F. 2007. Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. *J Autism Dev Disord,* 37**,** 367-73.

REDDIHOUGH, D. S., MARRAFFA, C., MOUTI, A., O'SULLIVAN, M., LEE, K. J., ORSINI, F., HAZELL, P., GRANICH, J., WHITEHOUSE, A. J. O., WRAY, J., DOSSETOR, D., SANTOSH, P., SILOVE, N. & KOHN, M. 2019. Effect of Fluoxetine on Obsessive-Compulsive Behaviors in Children and Adolescents With Autism Spectrum Disorders: A Randomized Clinical Trial. *Jama,* 322**,** 1561-1569.

STIGLER, K. A., MULLETT, J. E., ERICKSON, C. A., POSEY, D. J. & MCDOUGLE, C. J. 2012. Paliperidone for irritability in adolescents and young adults with autistic disorder. *Psychopharmacology (Berl),* 223**,** 237-45.

WASSERMAN, S., IYENGAR, R., CHAPLIN, W. F., WATNER, D., WALDOKS, S. E., ANAGNOSTOU, E., SOORYA, L. & HOLLANDER, E. 2006. Levetiracetam versus placebo in childhood and adolescent autism: a double-blind placebo-controlled study. *Int Clin Psychopharmacol,* 21**,** 363-7.