Essex Partnership University
NHS Foundation Trust

SECTION 13: DRUG USE IN LEARNING DISABILITIES

Formulary and Prescribing Guidelines

INTRODUCTION

Learning disability (LD), as defined by ICD (F70-F79) 2007, is a condition of arrested or incomplete development of the mind, which is especially characterised by impairment of skills (cognitive, language, motor, and social) during the developmental period, contributing to the overall level of intelligence. Retardation can occur with or without any other mental or physical condition.

13.1 Epilepsy in persons with a LD

Epilepsy is more prevalent in people with a LD than in the general population. About 20-30% of individuals who have a mild to moderate LD also have epilepsy and the more severe the LD; the more likely it is that a person will have epilepsy. There is also a correlation between the level of LD and severity of the presenting epilepsy. Around 20% of people with epilepsy also have a LD[1].

The seizure types/syndromes seen in learning disabilities are similar to the normal population; however there is a reversed ratio of primary generalised epilepsies to partial onset epilepsies in the two groups; with partial onset epilepsies being the most common seen in people with a learning disability. Epilepsy syndromes with multiple seizure types are also seen in the population with a learning disability more frequently than in the normal population. Approximately 60% of the general population will become seizure free on the first or second anti-epileptic drug (AED) used; this figure reduces to 40% in the learning disability population. This is due mostly to the increased ratio of partial onset seizures and also to the higher prevalence of the complex epilepsy syndromes[1].

The measurement of blood levels to monitor patients when more than one drug is used is not essential. A good history must be taken from the carers and the person with the LD. Follow ups must be regular with appointments being long enough to elicit symptoms and signs of pharmacodynamic and pharmacokinetic interactions. Where phenytoin is used, blood levels should be measured. It may also be useful where valproate is being added to, or withdrawn from, lamotrigine; and where lamotrigine is being used in pregnancy. It should be remembered that pharmacodynamic interactions are not reflected in blood levels, and that blood levels will not reflect the presence of active metabolite(s) of some medication(s). The key to management is in good history taking and clinical examination anticipating such problems. It is of paramount importance to optimise treatment with AEDs in this population as people with epilepsy and LD have a higher rate (compared to people with epilepsy without LD) of sudden death in epilepsy (SUDEP). Case-control studies have found that increased frequency of generalized tonic-clonic seizures, polytherapy, increased duration of epilepsy, and younger age at onset carry an increased risk for SUDEP. The likelihood of SUDEP increases with the severity of the epilepsy from about 1 per 1000 patient years to 1 per 250 patient years in the most severe cases. Several AEDs have had statistical increases in association with SUDEP including carbamazepine and lamotrigine. It is not clear whether this is a pharmacological factor or due to their use in severe epilepsies[2]. Concordance with medication, continued efforts to prevent tonic clonic seizures and avoidance of situations that reduce the seizure threshold, such as poor sleep, constipation and excess alcohol should be at the centre of efforts to prevent SUDEP in individual cases.

Where possible monotherapy with seizure freedom is the ideal management approach[2,3]. Combination therapy can be considered if seizures continue with attempts of monotherapy. If trials of combination therapy do not bring about worthwhile benefits,

revert to the regime (monotherapy or combination therapy) that has provided the best balance between tolerability and reducing seizure frequency. Seizure type, epilepsy syndrome, co-medication, co-morbidity, lifestyle and patient/carer preference should all be taken into consideration when selecting an AED.

Consistent supply to the child, young person or adult with epilepsy of a particular manufacturer's AED preparation is recommended, unless the prescriber, in consultation with the child, young person, adult and their family and/or carers as appropriate, considers that this is not a concern. Different preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles and care needs to be taken to avoid reduced effect or excessive side effects. Consult the summary of product characteristics (SPC) and British National Formulary (BNF) on the bioavailability and pharmacokinetic profiles of individual AEDs, but note that these do not give information on comparing bioavailability of different generic preparations.

Approved AED for Seizure control in persons with a LD

Drug[3]	Formulation[3]	Comments[3-5]
Carbamazepine	Tabs 100mg, 200mg, 400mg. M/R tabs (scored), 200mg, 400mg Liquid, 100mg/5mL Suppository, 125mg (=100mg tab), 250mg.	Licensed for use in generalised tonic-clonic and partial seizures. Not usually effective in absences (petit mal) and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients on carbamazepine with atypical absence. Controlled release preparations should be prescribed when possible.
Clobazam	Tabs 10mg Suspension 5mg/5ml, 10mg/5ml	Adjunct in epilepsy. During the treatment of epilepsy with benzodiazepines, including clobazam - consideration must be given to the possibility of a decrease in anticonvulsant efficacy (development of tolerance) in the course of treatment.
Clonazepam	Tabs 0.5mg, 2mg Oral drops 2.5mg/ml Oral solution 500microgram/5ml, 2mg/5ml Oral lyophilisate 500 microgram	Licensed for all clinical forms of epileptic disease and seizures in infants, children and adults, especially absence seizures (petit mal) including atypical absence; primary or secondarily generalised tonic-clonic (grand mal), tonic or clonic seizures; partial (focal) seizures with elementary or complex symptomatology; various forms of myoclonic seizures, myoclonus and associated abnormal movements
Ethosuximide	Syrup 250mg/5ml Caps 250mg	Licensed for absence seizures, myoclonic seizures but also as adjunctive therapy in atypical absence seizures. NB: complex partial seizures often misdiagnosed as absence epilepsy.
Gabapentin	Caps 100mg, 300mg, 400mg Tabs 600mg, 800mg Oral solution 50mg/ml	Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above. Also indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults & adolescents aged ≥ 12 years.
Lacosamide	Tabs 50mg, 100mg, 150mg, 200mg Syrup 10mg/ml	Indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolesecents and children from 4 years old with epilepsy. It is restricted for specialist use in refractory epilepsy.

Drug[3]	Formulation[3]	Comments[3-5]
Lamotrigine	Tabs 25mg, 50mg, 100mg, 200mg Dispersible tabs 2mg, 5mg, 25mg, 100mg	Adults and adolescents aged 13 years and above: a) adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures and b) seizures associated with Lennox-Gastaut syndrome (lamotrigine is given as adjunctive therapy but may be the initial AED to start with in Lennox-Gastaut syndrome). Children and adolescents aged 2 to 12 years: a) adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome and b) monotherapy of typical absence seizures.
Levetiracetam	Tabs 250mg, 500mg, 750mg, 1g. Oral solution 100mg/ml.	Licensed as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years with newly diagnosed epilepsy. Licensed as adjunctive therapy: a) in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy; b) in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy; c) in the treatment of primary generalised tonic-clonic seizures in adults & adolescents ≥ 12 years with Idiopathic Generalised Epilepsy
Oxcarbazepine	Tabs 150mg, 300mg, 600mg Suspension S/F 300mg/5ml	Licensed as monotherapy or adjunctive therapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures.
Phenobarbital	Tabs 15mg, 30mg, 60mg Elixir 15mg/5ml	Indicated for all types of epilepsy except absence seizures.
Phenytoin (Rarely used in LD)	Tabs 100 mg. Caps 25mg, 50mg, 100mg, 300mg. Suspension 30mg/5mL	Indicated for tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. **Consultant assessment/initiation only.**
Pregabalin	Caps 25mg 50mg 75mg, 100mg, 150mg; 200mg, 225mg, 300mg Oral solution 20mg/ml	Licensed for adjunctive therapy in adults with partial seizures with or without secondary generalisation.
Primidone	Tabs 50mg, 250mg Oral solution 25mg/ml	Indicated for all types of epilepsy except absence seizure. Primidone is largely converted to phenobarbital. An initial low dose is essential.
Tiagabine	Tabs 5mg, 10mg, 15mg	Indicated as add-on therapy for partial seizures with or without secondary generalisation where control is not achieved by optimal doses of at least one other anti-epileptic drug.
Topiramate	Tabs 25mg, 50mg, 100mg, 200mg Sprinkle capsules 15mg, 25mg, 50mg	Monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures. Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome.
Valproate	Tabs (crushable), 100mg. Tabs E/C 200mg, 500mg Oral solution, 200mg/5mL. Capsules M/R 150mg, 300mg Granules M/R 50mg, 100mg 250mg, 500mg, 750mg, 1000mg. Tablets M/R 200mg, 300mg, 500mg	Licensed for the treatment of generalized, partial or other epilepsy. Contraindicated in females of childbearing potential unless they meet the conditions of a Pregnancy Prevention Programme, It is subject to additional monitoring and all suspected adverse effects should be reported via the yellow card scheme.

Drug[3]	Formulation[3]	Comments[3-5]
Vigabatrin	Tabs 500mg Powder 500mg/sachet	Treatment in combination with other anti-epileptic drugs for patients with resistant partial epilepsy with or without secondary generalisation, that is where all other appropriate drug combinations have proved inadequate or have not been tolerated.
Zonisamide	Caps 25mg, 50mg, 100mg	Can be used as adjunctive treatment of l partial seizures with or without secondary generalisation in adults, adolescents and children aged 6 years and older. Monotherapy in the treatment of partial seizures, with or without secondary generalisation in adults with newly diagnosed epilepsy.

Prescribers of pregabalin and gabapentin should be aware that there is a risk of dependence and that they may be misused or diverted. [19] As of April 2019, because of a risk of abuse and dependence, pregabalin and gabapentin are scheduled under the Misuse of Drugs Regulations 2001 as schedule 3. They are therefore now subject to the prescription-writing requirements for schedule 3 controlled drugs, i.e. prescriptions must include the prescriber's address, patient's full name and address, NHS number, name of the drug, form of the preparation (e.g. tablets, capsules, even if only one form exists), strength of the preparation, dose to be taken, total quantity of the preparation to be supplied, in both words and figures, e.g. 'ten (10) capsules, signature of the prescriber (and to aid identification, the prescriber should also print their name in block capitals, followed by their professional registration number), and the date on which the prescription has been written.

- Valproate medicines must not be used in women or girls of childbearing potential unless a Pregnancy Prevention Programme is in place[19] and the conditions met, and only if other treatments are ineffective or not tolerated, as judged by an experienced specialist. Ensure all women and girls (and their parent, caregiver, or responsible person, if necessary) are fully informed of the risks and the need to avoid exposure to valproate medicines in pregnancy. Specialists must book in review appointments at least annually with women and girls under the Pregnancy Prevention Programme, check they are on highly effective contraception (taken without interruption), and re-evaluate treatment as necessary; explain clearly the conditions as outlined in the supporting materials (the "toolkit")[22] ;provide a "Patient Guide"[22] to girls (of any age) and women of childbearing potential (or their parent/caregiver/responsible person) who are started on or are continuing to use valproate medicines; and complete and sign the Annual Risk Acknowledgement Form (Annex 2)—a copy of the form must be filed in the patient's record, a copy given to the patient or patient/caregiver/responsible person, and a copy sent to their GP.
- As with all teratogenic medicines, pregnancy should be excluded before initiation on valproate medicines, with a negative plasma pregnancy test, confirmed by a healthcare professional. Women and girls of childbearing potential must use highly effective contraception if they are able to become pregnant (see guidance from Faculty of Sexual and Reproductive Health [FSRH] https://www.fsrh.org/news/fsrh-ceu-statement-on-contraception-for-women-using-known/). Methods of contraception considered 'highly effective' in this context include the long-acting reversible contraceptives (LARC): copper intrauterine device (Cu-IUD), levonorgestrel intrauterine system (LNG-IUS), and progestogen-only implant (IMP), and male and female sterilisation, all of

which have a failure rate of less than 1% with typical use (see guidance from FSRH for more about user-independent methods and failure rates). If a user-independent form is not used, two complementary forms of contraception including a barrier method should be used and regular pregnancy testing considered. Individual circumstances should be, in each case, evaluated when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures.[19]

If the patient becomes pregnant on valproate, consideration should be given to tapering the valproate down carefully, while introducing suitable alternative drug treatment.

The FDA has warned of a serious risk of death when benzodiazepines are used in combination with Opioid analgesic or cough preparations.[20]

13.1.1 NICE Clinical Guidelines

There is currently no specific guidance published from NICE which relates to the treatment of epilepsy in individuals with a LD. The NICE guidance below relates to epilepsy management in the general population.

CG 137, January 2012. Epilepsies: diagnosis and management.

Retigabine has been discontinued by the manufacturer due to limited usage[17].

NICE suggest that newer AEDs are reserved for children who have not benefited from treatment with the older AEDs (e.g. Carbamazepine or Sodium Valproate) or when they are unsuitable. Sodium Valproate should be the drug of choice in generalised and unclassifiable epilepsies and carbamazepine or lamotrigine in focal epilepsies[6].

NICE guideline NG144: Cannabis-based medicinal products [23] covers prescribing of cannabis-based medicinal products for severe treatment-resistant epilepsy. Applications for patient treatment using cannabis-based products must be made to the MMG.

13.1.2 Convulsive seizure (prolonged > 5min) rescue medication

Drug[3]	Formulation[3]	Comments[3-5]
Diazepam	Rectal suppository 2 mg/mL, 4 mg/mL	1 month - 2 yrs: 5mg 2yrs - 12yrs: 5-10mg >12 yrs: 10mg Repeat after 10-15 minutes if necessary

Drug[3]	Formulation[3]	Comments[3-5]
Midazolam (Note: Schedule 3 Controlled Drug)	Buccal liquid, midazolam 10mg/mL (-Epistatus) OR 5mg/ml (Buccolam)	. 1yr - 5yrs: 5mg 5yrs - 10yrs: 7.5mg >10 yrs: 10mg Repeat after 10-15 minutes if necessary

Status epilepticus should be treated as a medical emergency, and if the treatment with 10mg of rectal diazepam or midazolam given after a seizure has continued for 5 minutes, followed by a second dose of 10mg does not stop the seizure then emergency assistance from paramedics and/or general hospital should be sought without delay.

Buccal midazolam or rectal diazepam should ONLY be prescribed for use in the community for children, young people and adults who have had a previous episode of prolonged or serial convulsive seizures.

Buccal midazolam should be administered as a first-line treatment in children, young people and adults with prolonged or repeated seizures in the community. Rectal diazepam can be administered if preferred or if buccal midazolam is not available. If intravenous access is already established and resuscitation facilities are available, intravenous lorazepam can be administered.Instructions for use of buccal midazolam should be written up according to the individual needs of each patient.

There are currently two preparations of buccal midazolam available and a variation in prescribing preference across the various localities. New and existing patients within Bedfordshire & Luton and SE Essex should be prescribed Epistatus , while those in SW Essex should be prescribed Buccolam. Prescribers should be aware of the differing concentrations of the two preparations and to avoid any confusion, brand prescribing is encouraged.

13.2 Autism Spectrum disorders (ASD)

ASD is associated with a triad of impairments – display of restrictive repetitive activities (e.g. lining up objects in a particular order), a deficit in verbal and non-verbal communication (e.g. echolalia or mutism) and a deficit in reciprocal social interaction (e.g. can be markedly unaware of others and their feelings, and fail to develop peer relationships). These disorders are usually apparent below the age of 3 but may not be recognised for many years in some individuals.

In recent decades more individuals of normal intellectual ability are being recognised as having ASD. The co-morbidity of LD and ASD is significantly higher. Psychiatric co-morbidity is high – with co-existence of anxiety, affective disorders, tics, tourettes syndrome, ADHD, and catatonia. Epilepsy (seizure type depends on level of learning disability as described above) is also more common in this population.

Currently there is no single medication for ASD that alleviates symptoms in all three domains simultaneously. Targeting pharmacological interventions by identifying problem behaviours and the level of impairment these cause is essential. Standardised behaviour rating scales and adverse effect checklists are essential tools in monitoring progress[2]. It should be noted that many of the following studies refer to use of medication in children and adolescents.

13.2.1 Drugs used in ASD – for restrictive repetitive behaviours

The evidence for the use of fluoxetine in repetitive behaviour of autism is not well established. Hollander et al (2005) claimed that in a group of children and adolescents (N=45), low dose fluoxetine was superior to placebo with respect to reduction in repetitive behaviours of autism, as measured on the CY-BOCS compulsion scale[7]. The mean dose of fluoxetine was 9.9mg +/- 4.35 mg per day and the authors claim that there was no difference between active drug (at this dose) and placebo with respect to treatment emergent side effects.

However, more recently, fluoxetine, in the largest clinical trial ever conducted in patients with autistic disorder (N=158, aged 5-17), was branded as 'ineffective' against repetitive behaviour of autism. The study of fluoxetine in autism (SOFIA) concluded that there was no significant difference between fluoxetine and placebo with respect to this core domain[8].

In a recent Cochrane systematic review carried out to ascertain if treatment with an SSRI had an effect on core features of autism (including repetitive activities), and non-core features of autism, the authors concluded that there was no evidence to support the use of SSRIs in childhood autism[9]. Indeed, the authors claimed that there was, in children with autism, emerging evidence of harm. There was however, 'limited evidence, which is not yet sufficiently robust, to suggest effectiveness of SSRIs in **adults** with autism'.

When using fluoxetine to treat repetitive behaviours for children and adolescents with ASD, it has been generally found that much lower doses are required than the therapeutic antidepressant dose. It is advisable to use the liquid dose and begin at the lowest possible dose (2.5mg/day), monitoring for side effects[2]. The same monitoring requirements should be employed.

13.2.2 Drugs used in ASD – aggression

Horrigan et al evaluated the effects of risperidone on aggression, self-injury, explosivity and sleep hygiene in 11 male outpatients with autism. The optimal modal dose of risperidone was quoted at 0.5 mg twice daily and clinical improvement in the aforementioned areas was noted 'almost immediately'[10]. Weight gain was documented as the most serious side effect.

Risperidone was found to be effective in an open clinical study (of approximately 2 years duration), in 12 children (with autism and ADHD)[11]. Nine out of 12 children responded, with improvements especially noted in aggression, sleep and appetite. Risperidone was commenced at a dose of 0.5mg a day, and increased by 0.5mg per day every month. The final effective dose range was 1 - 3mg daily. The authors concluded that risperidone was safe and effective in this population long-term. Side effects noted included weight gain and sedation.

13.2.3 Drugs used in ASD – irritability

Positive results were reported in a placebo-controlled trial for treatment for irritability in adults with risperidone[12] by McDougle et al., 1998.

13.3 Aggression in persons with a LD

Treatment of aggression with psychotropics should be a measure of last resort after psychological and other interventions have been tried[18]. All attempts should be made to identify cause(s) of aggression such as pain (e.g. dental pain), infection (e.g. UTI), depression or changes in the environment (e.g. change of routine). If there is reason to believe that the aggression is related to lack of seizure control, valproate or carbamazepine may be tried.

If there is no epilepsy, lithium is an alternative. Craft et al., (1987) reported a 73% reduction in aggression/ self-mutilation in mentally challenged patients treated with lithium (at levels of 0.7 -1.0mmol/L) for 2 months[13]. 36% of the lithium treated group (N=22) recorded side-effects relative to only 20% in the placebo (N=20) group; but no side-effect in either group necessitated discontinuation. The authors claimed that the response was independent of gender and that all patients with difficult to control severe aggression/ self-mutilation should be considered for a trial of lithium. If lithium is prescribed serum creatinine should be measured to monitor for acute kidney injury[21].

In reality, most episodes of aggression not amenable to psychological or behavioural interventions are treated with antipsychotics e.g. risperidone. A study by Ruedrich et al., demonstrated that subjects with aggression without self-injurious behaviour had a significant decrease in the number of aggressive acts per month during a year of atypical treatment with risperidone, olanzapine or quetiapine but a high frequency of side effects especially weight gain[14].

The evidence base for antipsychotics in aggression associated with LD is weak. One set of authors found that neither risperidone nor haloperidol reduced aggression to a greater extent than that observed for placebo. In this trial all 3 subgroups showed substantial reduction in aggression at week 4, but the greatest reduction was in the placebo group[15].

Thus, if it is still considered necessary to use antipsychotics, it is important to specify target symptoms and monitor for efficacy, whilst monitoring for side effects. Should there be little or no improvement in target symptoms, then the antipsychotic(s) should be discontinued. The only licensed medication for children and adolescents is risperidone. Treatment of irritability in adults with ASD is reported in a placebo-controlled trail to respond in a similar way[2].

13.4 Self injurious behaviour (SIB) in persons with a LD

Self-injurious behaviour or self- mutilation has been defined as the deliberate destruction of body tissue without conscious suicidal intent[4]. Physical harm includes bruising, lacerations, bleeding, bone fractures/breakages and other tissue damage.

Mace and Mauk (1993) have suggested various clinical subtypes of SIB – with different neurotransmitters (for example, opiate, dopamine, serotonin, and noradrenaline) for the different forms of SIB[16]. Thus, different forms of SIB may be amenable to different types of psychotropics such as:

- Pain insensitive SIB (possibly amenable to an opiate- antagonist, naltrexone).

- SIB associated with stereotypy, and thus possibly amenable to antipsychotics.
- SIB associated with agitation when the SIB is interrupted, and thus possibly sensitive to SSRIs (or clomipramine).
- SIB associated with 'high arousal, for example, anxiety' and thus possibly sensitive to beta-blockers (such as propranolol).

13.4.1 Drugs approved in SIB in persons with a LD

See Annex 1 for detailed comments/evidence regarding the treatment options below.

- Antipsychotics
- SSRI antidepressants
- Lithium
- Naltrexone
- Propranolol

References

1. Epilepsy Society website; Epilepsy and learning disabilities, https://www.epilepsysociety.org.uk/learning-disabilities#.WgrOGU9LHIU (Accessed 14/11/2017)
2. South London & Maudsley NHS Foundation Trust Prescribing Guidelines 12th edition, Wiley Blackwell 2015
3. BNF online, current edition, Accessed 23/5/2018.
4. The Frith Prescribing Guidelines for Adults with Intellectual Disability) 2015 Wiley Blackwell
5. Summary of Product Characteristics for Individual Drugs (Accessed November 2017). http://www.medicines.org.uk/EMC ; sodium valproate (Epilim) accessed 23/5/2018.
6. NICE CG137, January 2012. Epilepsies: diagnosis and management. http://www.nice.org.uk/Guidance/cg137 (Accessed November 2017)
7. Hollander et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviours in childhood and adolescent autism. Neuropsychopharmacology.2005 Mar;30(3):582 http://www.ncbi.nlm.nih.gov/pubmed/15602505
8. ACTN Trial: Study of Fluoxetine in Autism (SOFIA) Sponsor: Neuropharm Group Plc http://www.autismspeaks.org/science/programs/ctn/
9. Williams K, Wheeler DM, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD004677. DOI: 10.1002/14651858.CD004677.pub2 http://www2.cochrane.org/reviews/en/ab004677.html
10. Horrigan J. P. et al. Risperidone and explosive autism. J Autism Dev Disord 1997; 27 (3): 313-323. http://www.ncbi.nlm.nih.gov/pubmed/9229261
11. Eapen V et al. Risperidone treatment in 12 children with Developmental Disorders and Attention Deficit/Hyperactivity Disorder 2005. Prim Care Companion J Clin Psych; 7(5): 221-224 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1257406/

12. Mc Dougle CJ et al. A double-blind placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. Arch Gen Psychiatry 1998; 55:633-641
13. M Craft et al. Lithium in the treatment of aggression in mentally handicapped patients. A double-blind trial 1987. The British Journal of Psychiatry; 150: 685-689 http://bjp.rcpsych.org/cgi/content/abstract/150/5/685
14. Ruedrich SL et al. Atypical antipsychotic medication improves aggression, but not self-injurious behaviour, in adults with intellectual disabilities. J Intellect Res; 52:132-140
15. Tyrer P et al. Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disability: a randomised controlled trial. Lancet. 2008 Jan 5; 371(9606):57-63. http://www.ncbi.nlm.nih.gov/pubmed/18177776
16. Mace F C et al. Bio-behavioral diagnosis and treatment of self-injury 1995. Mental Retardation and Developmental Disabilities Research Reviews Volume 1, Issue 2, 104–110 http://onlinelibrary.wiley.com/doi/10.1002/mrdd.1410010206/abstract
17. NICE TA 232 Retigabine for the adjunctive treatment of partial onset seizures in epilepsy. Accessed November 2017.18. NICE NG11 Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges http://www.nice.org.uk/guidance/ng11 (Accessed November 2017.)
19 Drug Safety Update. Valproate medicines (Epilim▼, Depakote▼): contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met. Medicines and Healthcare products Regulatory Agency. Published 24 April 2018. Accessed 23/5/2018. https://www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-contraindicated-in-women-and-girls-of-childbearing-potential-unless-conditions-of-pregnancy-prevention-programme-are-met
20. http://www.fda.gov/Drugs/DrugSafety/default.htm Accessed September 2016
21 Guidance for Mental Health Professionals on the management of Acute Kidney Injury
22. Guidance. Valproate use by women and girls. Information about the risks of taking valproate medicines during pregnancy. Toolkit. Medicines and Healthcare products Regulatory Agency. Last updated 9 April 2019. Accessed 23/5/2019. https://www.gov.uk/guidance/valproate-use-by-women-and-girls
23. NICE NG144: Cannabis-based medicinal products. Published date: 11 November 2019. Accessed 4/5/2020.

Annex 1

Further information for drugs used in self-injurious behaviour

Naltrexone

Not licensed for the treatment of self-injurious behaviour but instead indicated for the adjunctive prophylactic therapy in the maintenance of detoxified, formerly opioid-dependent patients (at a starting dose of 25 mg daily for one day, increasing thereafter to 50mg daily). It is therefore contra-indicated in patients who are dependent on opioids or currently taking opioid-containing medicines. Additionally, it is also contra-indicated in patients with acute hepatitis/liver failure. LFTs should be monitored before and during treatment.

Naltrexone has been the subject of 2 Cochrane reviews[1,2]:

a) 'Efficacy and Safety of naltrexone use in paediatric patients with autistic disorder[1], and

b) 'The use of opioid antagonists for recurrent self-injurious behaviour[2].

In a) – the authors concluded that 'children affected with AD, particularly those with self-injurious behaviour, may benefit from naltrexone (starting with a low dose such as 0.5 mg/kg daily, and titrating upwards according to response and/or adverse effects).' It was also reported, in this review, that short term studies did not report any adverse effects.

In b) – the authors stated that 'there was a positive response to naltrexone in one half of patients, with most showing 30 to 50 % reduction in SIB'. (50% of patients were under 18 years of age.) Additionally, they claimed that naltrexone was 'well-tolerated in doses of up to 1.5 mg/kg/day'.

Irrespective of the aforementioned, the only prospective, double-blind, placebo-controlled study to be carried out (with naltrexone, in patients with autism and SIB) found that naltrexone was no better than placebo, and at a dose of 50 mg daily was found to be worse than placebo with respect to CGI[3].

In short, as both Cochrane reviews recommend – further large, long-term RCTs are needed to fully elucidate the efficacy and safety of naltrexone in SIB.

However, one challenging behaviour foundation website[3] has recommended opiate antagonists (naltrexone (and the parenteral opiate antagonist, naloxone)) as the only medication that has consistently been found to ameliorate self-injury.

Lithium

Lithium is actually licensed for the treatment of aggressive or self-mutilating behaviour[4], but the evidence base for its indication in self-injurious behaviour is sparse. The frequently quoted paper by Craft et al[5] attests to the efficacy of Lithium in aggression in 42 LD patients (at serum levels of 0.7 – 1.0 mmol/Litre) by 2-8 weeks of therapy. Although the authors conclude that 'Lithium therapy is therefore worth a 2-month trial in any patient whose repeated aggression or self-mutilation is proving difficult to control' – it is difficult to tell if any of the patients in this trial actually had SIB. (The trial was, however, double-blind and placebo-controlled.)

In one retrospective review[6], 17 patients (with 'aggression and SIB') who had been treated with either propranolol (N=6) or Lithium (N=11) were reported as having 'equal reductions

in both behaviours with either drug' 3 months after commencement of the beta-blocker or mood stabilizer.

In a single case report, Cooper and Fowlie report on the successful use of Lithium in a woman with Learning Disability exhibiting SIB[7]. The authors were at pains to point out that the level of SIB in this patient was 'very severe'.

The above reports emanate from the 1970's and 1980's – more recently (2008) a review by Deb et al[8], found 3 studies relating to Lithium's activity in the 'management of behavioural problems in adults with LD'. Out of a total of 3 studies, Lithium was found to improve aggression in 47-73% of participants but in one study (out of the 3) there was no improvement in SIB.

Propranolol

As for lithium – the data pertaining to efficacy in SIB is limited.

Reports also refer to efficacy in the joint presentation of 'aggression and self-injurious behaviour'. In one case report[9], a multiply handicapped adolescent with severe SIB showed 'gradual but steady reduction in self-injury over 12 months' with propranolol. (The dose utilised was 300mg/day – a dose that is within the UK recommended maximum daily dose but would necessitate BP, HR, and possibly ECG monitoring).

There are no Cochrane reviews on the use of propranolol in self –mutilation but only one referring to the efficacy of beta-blockers in acquired brain injury[10].

Antipsychotics

According to a recent Cochrane review, risperidone was found to be statistically superior to placebo ($p<0.001$) in reducing self-injurious behaviour (along with physical aggression and property destruction) from the 4th week of administration in autism spectrum disorder. This efficacy continued through to week 8[11].

However, the authors (of the review) pointed out that [although] 'risperidone can be beneficial in some features of autism, there are limited data available from studies with small sample sizes.

In addition, there lacks a single standardised outcome measure allowing adequate comparison of studies, and long-term follow-up is also lacking. Further research is necessary to determine the efficacy of risperidone in clinical practice [in ASD]'.

Olanzapine has also been reported to reduce the level of 'aggressive, self-injurious, and destructive and disruptive behaviours' in approximately 20 patients with LD. The sample mean age was approximately 42.7 years, on a mean dose of 9.1 mg/day. The net effect was to allow concomitant reduction in other (conventional) antipsychotics[17]. Expected adverse drug reactions included significant weight gain, sedation and constipation.

Another study suggested that olanzapine can reduce stereotypic SIB[18].

SSRI antidepressants

In a (Cochrane) systematic review carried out to ascertain if treatment with an SSRI had an effect on core features of autism, and non-core features of autism (including self-injurious behaviour), the authors concluded that there was no evidence to support the use of SSRIs in childhood autism. Indeed, the authors claimed that there was, in children with

autism, emerging evidence of harm[12]. There was however, 'limited evidence, which is not yet sufficiently robust, to suggest effectiveness of SSRIs in adults with autism'.

It is noteworthy that the target symptom of 'self-mutilation' was not assessed by the actual trials included in the systematic review. Additionally, the authors included trials with 'fenfluramine' which they classify as an SSRI – in the UK, this medicine (now discontinued because of association with valvular heart disease) was classified as an amphetamine.

Case reports citing efficacy of SSRIs, in patients with LD and self-injurious behaviour do exist with respect to fluoxetine and fluvoxamine.

Two cases employing serotonergic antidepressants (sertraline and clomipramine) for SIB were positive and the results were maintained over several months of follow up[13].

One report highlights the efficacy of citalopram in a case of 'unusually devastating self-injurious behaviour' in a 30 year old male, whose SIB was unresponsive to antipsychotics[3]. The omission of said citalopram (20 mg/daily) for a few days resulted in rapid re-appearance of the self-mutilation, and subsequent disappearance of this behaviour upon re-institution of the SSRI.

Cook et al., (1992) used fluoxetine, in doses between 20 and 80 mg per day, to treat a number of maladaptive behaviours in children and adults with learning disabilities. Eight people had severe self- injurious behaviour, and of these three showed a reduction or cessation of self- injury when fluoxetine was prescribed[14].

Markowitz (1992) reported a marked reduction in severe self-injurious behaviour among 17 out of 21 people with severe learning disabilities following fluoxetine treatment[15].

Lewis et al., (1996) compared clomipramine (predominantly a serotonin reuptake inhibitor) with placebo in a double-blind trial involving eight people with severe or profound learning disabilities. Six showed a significant (50% or greater compared to placebo) reduction in their severe self- injurious behaviour. Clomipramine also reduced stereotypies and compulsions[16]. Adverse effects included tachycardia, constipation, increased appetite, agitation and a seizure, but were only problematic for two of the people taking part.

The information included within this appendix is but no means exhaustive and readers are reminded to consult a more comprehensive and the most up to date references when making clinical decisions.

References

1. Elchaar G M, Maisch N M, Augusto L M, Wehring H J. Efficacy and safety of naltrexone use in paediatric patients with autistic disorder. Annals of pharmacotherapy.2006;40(6):1086-1095 http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12006003704/frame.html
2. Buzan R D, Thomas M, Dubovsky S L, Treadway J. The use of opiate antagonists for recurrent self-injurious behaviour. Journal of Neuropsychiatry and Clinical Neurosciences.1995; 7(4):437-444.http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-11995003155/frame.html
3. Willemsen-Swinkels S et al. Failure of Naltrexone Hydrochloride to Reduce Self-Injurious and Autistic Behaviour in Mentally Retarded Adults**.** Arch Gen

Psychiatry. 1995; 52(9):766-773.http://archpsyc.ama-assn.org/cgi/content/abstract/52/9/766
4. British National Formulary online, November 2017.
5. M Craft et al. Lithium in the treatment of aggression in mentally handicapped patients. A double-blind trial 1987. The British Journal of Psychiatry; 150: 685-689 http://bjp.rcpsych.org/cgi/content/abstract/150/5/685
6. Luchins DJ, Lithium and propranolol in aggression and self-injurious behaviour in the mentally retarded. Psychopharmacol Bull. 1989;25(3):372-5. http://www.ncbi.nlm.nih.gov/pubmed/2626515
7. Cooper A F et al. Control of gross self-mutilation with Lithium Carbonate. British Journal of Psychiatry 1973. 122; 370-371.
8. Deb S et al. The Effectiveness of mood stabilizers and antiepileptic medication for the management of behaviour problems in adults with intellectual disability: a systematic review. Database of Abstracts of reviews of effects (DARE). http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2788.2007.00965.x/full
9. Lang C, Remington D. Treatment with propranolol of severe self-injurious behaviour in a blind, deaf, retarded adolescent. J Am Acad Child Adolesc Psychiatry. 1994 Feb;33(2):265-9. http://www.ncbi.nlm.nih.gov/pubmed/8150799
10. Fleminger S et al. Pharmacological management for agitation and aggression in people with acquired brain injury. Cochrane Database Syst Rev. 2006 Oct 18; (4):CD003299. http://www.ncbi.nlm.nih.gov/pubmed/17054165
11. Jesner OS, Aref-Adib M, Coren E. Risperidone for autism spectrum disorder. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD005040. DOI: 10.1002/14651858.CD005040.pub2 http://www2.cochrane.org/reviews/en/ab005040.html
12. Williams K, Wheeler DM, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD004677. DOI: 10.1002/14651858.CD004677.pub2 http://www2.cochrane.org/reviews/en/ab004677.html
13. Luiselli J.K., Blew P., Thibadeau S.Therapeutic effects of long-term efficacy of antidepressant medication for people with developmental disorder: behavioural assessment in treatment-resistant aggression and self-injury. Behav Modif 2001; 25:62-78
14. Cook. E. H., Rowlett, R., Jaselskis, D. 0. et al (1992) Fluoxetine treatment of children and adults with autistic disorder and mental retardation. Journal of the American Academy of Child and Adolescent Psychiatry. 31.739-745.
15. Markowitz. P. I. (1992) Effect of fluoxetine In the developmentally disabled. A preliminary study Journal of Clinical Psychopharmacology. 12. 27-31
16. Lewis, M. H., Bodfish, J.W., Powell, S.B., et al (1996) Clomipramine treatment for self-injurious behaviour of individuals with mental retardation a double-blind comparison with placebo. American Journal of Mental Retardation. 100.654-665
17. Janowsky DS, Barnhill LJ, Davis JM. Olanzapine for self-injurious, aggressive, and disruptive behaviours in intellectually disabled adults: a retrospective, open-label, naturalistic trial. J Clin Psychiatry. 2003 Oct; 64(10):1258-65 http://www.ncbi.nlm.nih.gov/pubmed/14658977

18. McDonough M., Hillary J., Kennedy N. Olanzapine for chronic stereotypic self-injurious behaviour: a pilot study in seven adults with intellectual disability. J Intellect Disabil Res 2000; 44:677-684
19. Advice for prescribers on the risk of the misuse of pregabalin and gabapentin https://www.gov.uk/government/publications/pregabalin-and-gabapentin-advice-for-prescribers-on-the-risk-of-misuse (Accessed November 2017)

Annex 2

Annual Risk Acknowledgement Form
VALPROATE HAS RISKS IN PREGNANCY

Name of valproate user: _____ **Date of Birth:** _____

Identification (NHS or hospital) number: _____

Name and role of specialist: _____

Signature of specialist and date: _____

Name of valproate user's GP: _____

Children exposed to valproate in utero have a very high risk for congenital malformations and neurodevelopmental disorders. Valproate is therefore contraindicated in women of childbearing potential unless the conditions of 'prevent', the pregnancy prevention programme are fulfilled.

The specialist must provide this form to girls and women of childbearing potential treated with valproate (Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Orlept, Syonell, Valpal) - or to their "responsible person": a parent/legal guardian or person capable of giving consent on behalf of patients who are minors or without the capacity to make an informed decision or person acknowledging that the treatment is in the best interests of the patient.

There are three steps needed to complete this form:

Step 1 – Decide if the patient needs to be on 'prevent' – the valproate pregnancy prevention programme

Step 2 – 'prevent' applies to this patient- she is of childbearing potential and at risk of pregnancy

Step 3 – Your patient needs to complete this section to confirm they understand the risks of valproate in pregnancy

WARNING: Prescribing valproate to a woman of childbearing potential without the pregnancy prevention programme conditions being fulfilled is contraindicated and represents an unlicensed use of the drug. Use of valproate during pregnancy for bipolar disorder, and during pregnancy for epilepsy (unless there is no suitable alternative treatment), are both unlicensed. This is the case even when treatment is based on an informed choice made by the patient.

Prescribers are expected to follow the General Medical Council's guidance in *"Good practice in prescribing and managing medicines and devices"*. You must document in the patient's clinical record your reason for unlicensed use, that you have informed the patient of the unlicensed use and its associated risk.

This form expires on _____ **(12 months after completion).**

Complete a new form at each annual review.

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines that appear.

SAGB.VPA.15.12.1440c(2) March 2019

Annual Risk Acknowledgement Form
VALPROATE HAS RISKS IN PREGNANCY

Step 1 – Decide if the patient needs to be on 'prevent' – the valproate pregnancy prevention programme

- Women of childbearing potential (from menarche to menopause) who are taking any medicine containing valproate, regardless of the indication, should fulfil all the requirements of **'prevent'**.
- The only exception is when you (the specialist) consider that there are compelling reasons to indicate that there is no risk of pregnancy.
- The absence of risk of pregnancy may be permanent (e.g., post-menopausal patients or those after hysterectomy) and in this case the risk does not need to be discussed in the next annual review and the requirements of **'prevent'** do not apply.
- If the absence of risk is subject to change (e.g., the patient is pre-menarchal), the date for the next annual discussion of the risks must be documented and the patient or the patient's family/carers asked to contact you rapidly if the situation changes before the next annual review in order to bring this review forward.
- Girls who have not yet reached menarche **DO NOT** need to be on **'prevent'**, but they and their responsible person need to be aware of the risks for the future. You should provide a copy of the Patient Guide, and remind the responsible person to contact the specialist or GP to arrange for review of treatment as soon as menarche occurs.

If you consider there is a compelling reason that indicates there is no risk of pregnancy, record this here. **If appropriate, you and your patient should still complete the rest of the form** so that your patient and/or their responsible person is aware of the risks if their situation were to change in the future.

To be completed by the specialist when they consider a Pregnancy Prevention Programme (PPP) is not needed
The requirements of **'prevent'**, the valproate pregnancy prevention programme, are not necessary because there are compelling reasons to indicate that there is no risk of pregnancy, because (*tick* which applies):
☐ the patient has not yet reached menarche. I have informed the patient and family to inform me if this changes before the next annual review which is due on *(insert date)*:
☐ the absence of pregnancy risk is permanent for the following reason *(insert reason)*:
☐ I consider that sexual activity that could lead to pregnancy will not occur before the next annual review because *(insert reason)*:
☐ I have given the patient or responsible person a copy of the Patient Guide
Signature of patient or responsible person to confirm:

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines that appear.

SAGB.VPA.15.12.1440c(2) March 2019

Annual Risk Acknowledgement Form
VALPROATE HAS RISKS IN PREGNANCY

Step 2 – 'prevent' applies to this patient- she is of childbearing potential and at risk of pregnancy

This form confirms that you have discussed the risks with girls, women of childbearing potential and their responsible person (if applicable), and you are acting in compliance with the pregnancy prevention programme.

You need to:

- Explain the risks of valproate in pregnancy and ensure these are understood.
- Give your patient (or their responsible person) a copy of the Patient Guide.
- Complete all parts of this form, keep the original in the patient record and provide a copy to the patient, her responsible person (if appropriate), and to her GP.
- Arrange a follow-up appointment at least every year to review the need for continued treatment with valproate and compliance with **'prevent'**.

To be completed and initialled by the specialist	Initials
I confirm that the patient needs valproate because: • her condition does not respond adequately to other treatments, or • she does not tolerate other treatments, or • she is undergoing a treatment change from valproate	
I confirm I have discussed the following with the patient:	
Valproate must not be used during pregnancy (except in rare situations in epilepsy for patients who are resistant or intolerant to other treatments)	
The overall risks in children exposed to valproate during pregnancy are: • an approximately 10% chance of birth defects • a 30% to 40% chance of a wide range of early developmental problems that can lead to learning disabilities.	
The conditions of the pregnancy prevention programme must be fulfilled	
The need for regular (at least annual) review of the need to continue valproate treatment by a specialist	
The need for effective contraception, without interruption, throughout treatment with valproate	
The need to arrange an appointment with her specialist as soon as she is planning pregnancy to ensure timely discussion, and a timely switch to an alternative treatment before stopping contraception and conception occurring.	
The need to contact her GP immediately for an urgent review of her treatment in case of suspected or inadvertent pregnancy.	
The need for a negative (ideally serum) pregnancy test result at start and if needed thereafter	
I confirm I have given the patient or responsible person a copy of the Patient Guide	
In case of pregnancy, I confirm that:	
• We have discussed options for switching treatment	
• She is fully aware of the risks of pregnancy, and has had the opportunity for counselling about the risks	
• I have given the patient or responsible person a copy of the Patient Guide	

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines that appear.

SAGB.VPA.15.12.1440c(2) March 2019

Annual Risk Acknowledgement Form
VALPROATE HAS RISKS IN PREGNANCY

Step 3 – Your patient needs to complete this section to confirm they understand the risks of valproate in pregnancy

If you use valproate while you are pregnant, your future child has significant risk of serious harm.

Completing this form confirms that you (or your responsible person) understand the risks of using valproate during pregnancy, and what method of contraception you will use to prevent becoming pregnant during treatment.

To be completed and signed by the patient or their responsible person	Initials
I have discussed the following with my specialist and I understand:	
√ Why I need valproate rather than another medicine	
√ That I should visit a specialist regularly (at least once a year) to review whether valproate remains the best option for me	
√ The risks in children whose mothers took valproate during pregnancy are: • 1 out of 10 children will have physical birth defects • 3 to 4 out of 10 children will have early developmental problems that can lead to significant learning disabilities	
√ That I have had a pregnancy test (if advised by my doctor/specialist)	
√ Why I must use effective contraception, without stopping or interruption, at all times while taking valproate	
√ The options for effective long-term contraception (or a consultation has been planned with a professional who can give me advice)	
√ The need to consult my specialist or GP as soon as I start thinking about becoming pregnant. This is to make sure I have time to switch to another treatment before I come off contraception	
√ That I should request an urgent GP appointment if I think I am pregnant	
√ I have been given a copy of the Valproate Patient Guide and know where to find more information	
In case of pregnancy, I confirm that: √ Options for switching treatment have been considered √ I am fully aware of the risks and have had the opportunity to have counselling about the risks	

Name of patient: _____

Name of responsible person (if applicable): _____

Signature of patient (or responsible person) and date: _____

Effective contraception is essential while taking valproate.

At least one highly effective method of contraception (preferably a user independent form such as an intrauterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case. When choosing the contraception method involve the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhoea she must follow all the advice on highly effective contraception.

More information can also be found online at www.medicines.org.uk by entering "valproate" in the search box and then clicking on "Risk Materials" next to any of the medicines that appear.

SAGB.VPA.15.12.1440c(2) March 2019