ISSN 1391-0736

The Sri Lanka Prescriber

June 2010; Volume 18, No. 2

CONTENTS

The Sri Lanka Prescriber *is sponsored by the State Pharmaceuticals Corporation of Sri Lanka as a service to the medical profession.*

The Sri Lanka
Prescriber

Copies of the *Sri Lanka Prescriber* and inquiries from M. P. Kuruppu, Deputy General Manager, Marketing, and Ms Sujathi Jayaratne, Promotional Manager (Telephone 2421833), State Pharmaceuticals Corporation, P. O. Box 1757, 75, Sir Baron Jayathilake Mawatha, Colombo 1.

Price per copy Rs 50.00 (students Rs 25.00). Personal callers may also obtain copies from the Departments of Pharmacology at the Medical Faculties in Colombo, Galle and Sri Jayewardenepura.

Published by

Department of Pharmacology
Faculty of Medicine
271, Kynsey Road, Colombo 8, Sri Lanka.
Telephone: + 94 11 2695300 Ext 315
E-mail: phrm_cmb@hotmail.com
and
State Pharmaceuticals Corporation
75, Sir Baron Jayathilake Mawatha, Colombo 1.
Telephones + 94 11 2320356-9
Fax: + 94 11 447118
E-mail: prmanager@spc.lk Web site: www.spc.lk

Printed by

Ananda Press
82/5, Sri Ratnajothi Saravanamuttu Mawatha,
Colombo 13.
Telephone: + 94 11 2435975
E-mail: anpress@sltnet.lk

Cover picture

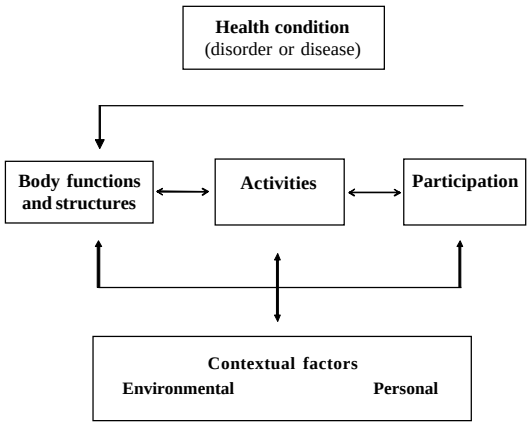
The Marshall apothecary

Enabling children with disabilities through early identification and intervention

Introduction

Over 200 million children are estimated at present to be disabled globally. Most of them remain a forgotten population within many societies. Delayed diagnosis and lack of appropriate services are two principal reasons for their marginalisation. In year 2002 the WHO brought in a broader and more dynamic definition for disability; the International Classification of Functioning Health and Disease (panel 1). According to this, environmental and personal factors significantly contribute towards disabilities in children in addition to the defective body function and structure (impairment). These influence the activity and participation of a child and may result in disablement within the society. This article will discuss a holistic management approach for such children with an aim to optimise their functioning in the society.

Panel 1. ICF (WHO 2002)



What are common childhood disabilities?

Disabilities are broadly categorised into five types: physical, communication, visual, cognitive and behavioural. Physical disabilities are estimated to be the commonest, yet many cognitive and behavioural disabilities remain unnoticed.

Panel 2. Why is early detection important?

- The capacity to learn and acquire new skills by the developing brain is maximal from 0-7 years.
- Beyond this age the underutilised neurons involute.
- Therefore early recognition of impairments and appropriate stimulation will help the child to develop to the maximal capacity.

How to identify a child with disabilities?

A child may present to a clinician in any of the following ways.

1. High risk infant/child
   a. Infant with a history of neonatal complications, eg. extreme preterm, hypoxic ischaemic encephalopathy.
   b. Children with genetic/chromosomal disorders, eg. trisomy 21.
   c. Child with a history of infective, inflammatory or traumatic insult to the central nervous system, eg. post-encephalitic, subdural haemorrhage.
2. Children detected during routine assessments, eg. delayed developmental milestones at the child welfare clinic.
3. Children detected to have educational and /or behavioural problems at schools, eg. attention deficit hyperactivity disorder, dyslexia.

These children can be missed because Sri Lanka does not have a good surveillance system in place, and it is imperative for the clinicians to have a high degree of suspicion.

In each child who is suspected to have a disability the following aspects are essential in the assessment.

1. Arriving at a clinical diagnosis.
2. Developmental assessment.
3. Assessment of social and environmental factors.

1. Clinical diagnosis

When approaching children a good history and examination remain the gold standards. The origin of the problem and its progression are important to arrive at a specific causative diagnosis. Most disabilities result from neurological dysfunction, yet musculoskeletal pathologies, metabolic causes or psychosocial issues should be considered.

The following examples illustrate the diverse causations.

1. A six-month old girl has no head control. She was resuscitated at birth. On examination all four limbs are spastic and reflexes are exaggerated.

   Diagnosis: Spastic quadriplegic cerebral palsy due to hypoxic ischaemic encephalopathy.

2. An eight-year old boy who was an attentive student for the last three years is withdrawn and pays less attention to school work this term. His mother sought employment in the Middle East recently and he lives with his aunt.

   Diagnosis: Psychological deprivation, but it is important to exclude pathological causes.

A detailed birth history, past medical history and family history will help the clinician to arrive at a clinical diagnosis. Though it is important not to miss any treatable developmental impairments (eg. congenital hypothyroidism) it is important to be aware that it is not possible to arrive at a definitive diagnosis in the majority of children with disabilities. This is not only due to the lack of advanced diagnostic tests such as detailed genetic and metabolic assays in Sri Lanka, but also because most disabilities arise from unknown aetiologies, limiting the treatment options.

Yet all children with an impairment need early recognition and management to minimise their disability within the society irrespective of the clinical diagnosis. So the development and social history become the cornerstone to address the functional needs of the child and the family.

2. Developmental assessment

Routine developmental screening during any encounter with a child is the best tool for early detection of impairments in children. The Child Health Development Record (CHDR) is a useful guide to parents, and helps health workers to identify the high risk babies. All high risk babies need close follow up by health workers competent in carrying out a simple developmental screening test. When a child is unable to reach a milestone at the 90th centile age limit for that skill the clinician should make an urgent referral to a paediatrician for a detailed clinical evaluation (panel 3). Specific assessments and investigations may be helpful to arrive at an aetiological diagnosis, with many limitations (panel 4).

Panel 3. 90th centile ages in developmental milestones

1. Responsive smile: 3 months
2. Head control: 4 months
3. Reaches for objects: 6 months
4. Sits alone: 9 months
5. Consonant babbling: 8 months
6. Recognisable words: 18 months
7. Walks alone: 18 months

Panel 4. Some useful investigations

1. T4/TSH
2. Hearing and visual assessment
3. Urine for metabolic screen
4. Karyotyping
5. Imaging of the brain

3. Assessment of social and environmental factors

In all children a detailed social history will show the level of activity and participation of a child, deciding the level of disablement in the society (home and school). This is also helpful to understand the family perceptions.

Panel 5. Essential components in the social history

1. Who takes care of the child most of the time?
2. How do other members of the family relate to the child?
3. Where does the child spend time mostly?
4. Does the family attend social functions?

   Does the child accompany them during these?
5. Is there any family disharmony due to this child?
6. What do parents feel about the future of this child?
7. Are there any environmental modifications at home?

Principles of management

The main objective is to ensure the child's fullest participation in the society. Hence the views of the family and the child take precedence over the clinician's.

1. Ideally a team of professionals needs to involve. a paediatrician, rehabilitation worker, physiotherapist, occupational therapist, speech and language therapist, teacher, social worker, and other specialists according to the need of each child, eg. neurologist, orthopaedic surgeon etc.

2. Explain the condition and prognosis to the parents, and plan the management together with them. Prioritise the requirements of the child and the family to ensure success and sustainability of the care program.

3. Draw up a plan that will equally recognise the rehabilitation, social and educational needs of a child in addition to medical needs.

4. Train parents to carry out home-based simple rehabilitation.
    a. Encourage correct posture and movements.
    b. Stimulate children through play.
    c. Focus on activities of daily living, eg. dressing, toileting, feeding etc.
    d. Ensure home modifications, eg. a ramp with a wooden plank.
    e. Encourage production of simple devices within the community, eg. a corner chair could be made by the local carpenter if drawings are provided.

5. Develop a good network among the social and educational institutions in the area. Liaise with the community based health, social and educational workers.
    a. Public health midwife and the medical officer of health (MOH) will provide information about the community based resources.
    b. A social worker and a child development officer attached to each divisional secretariat will assist the families in providing financial aid, assistive devices and vocational training.
    c. Refer to the local educational authorities at the appropriate age for schooling. Some pre-schools and schools in Sri Lanka practice inclusive education following global trends.

6. Attend to health and medical needs.
    a. Ensure continuous supply of regular medications, eg. antiepileptics
    b. Arrange for immunisation. Most children with disabilities can be immunised except for some few contraindications, eg. children with progressive neurological disorders or children with recurrent seizures.
    c. Ensure adequate nutrition.
    d. Look for other co-morbidities such as gastro-oesophageal reflux, constipation, recurrent wheezing and treat accordingly.
    e. Prevent skin infestations and dental caries.
    f. Assess risks for accidental and non-accidental injuries.

7. Explore avenues of income generation and empowerment for families. Local and national governmental and non-governmental organizations are useful resources.

8. Advocate developing positive attitudes about disabilities among communities and prevention of impairment.

Conclusions

Children with disabilities are a globally overlooked population. It is important to identify these children at an early stage as early intervention is imperative for a better outcome. When managing them it is essential to offer a holistic package to children and their families to achieve maximum functioning capacity within the society. Clinicians must liaise with the community-based health, educational and social workers to accomplish these goals.

Further reading

1. WHO, 2001. *International Classification of Functioning, Disability and Health.* Geneva,WHO. 3-30.
2. Zinkin P, McConachie H eds. Disabled Children and Developing Countries. London: Mc Keith Press. 1995.
3. Egan DF. Clinics in developmental medicine No. 112, Developmental examination of infants and preschool children. Oxford: Mc Keith.1990.
4. Law M, Petrenchik T, King G, Hurley P. Perceived environmental barriers to recreational, community, and school participation for children and youth with physical disabilities. *Archives of Physical Medicine and Rehabilitation* 2007; **88**: 636-42.
5. Helander E. Prejudice and dignity: an introduction to community based rehabilitation. A service delivery system for CBR. UNDP; 1994.

Dr. Samanmali P Sumanasena, MBBS, DCH, MD, MSc, MRCPCH, *Senior Lecturer in Paediatrics and Consultant Paediatrician, Faculty of Medicine, Colombo.*
Email: <paedcmb@gmail.com>
Conflicts of interest: none.

Management of type 1 diabetes mellitus in children

Introduction

There are two main types of diabetes mellitus in children. Type 1 diabetes (T1DM) is the commonest and is autoimmune in origin. Although not as common as in the developed countries, the incidence is increasing in Sri Lanka. Type 2 diabetes (T2DM) is associated with obesity, and childhood obesity is increasingly evident in Sri Lanka, which will give rise to an increase of T2DM in children in the near future.

Management of T1DM in children

Due to the autoimmune nature of the disease, the destructive process continues relentlessly over a variable period of time until there is no endogenous insulin secretion.

There is no treatment at present to halt this progression. Hence the aim is to control the disease, ensure a happy childhood, and minimise long term complications.

Principles of management

Management involves the entire family. The aspects that need particular attention are:

- Education of parents and the child about the disease, and importance of follow up
- Insulin therapy and diet
- Physical activity
- Monitoring glycaemic control
- Management during an illness
- Informing class teacher/close friends
- Screening for complications
- Puberty, adolescence and future as an adult/fertility
- Services of a diabetic nurse educator and social worker
- Psychological support for parents and the child

Insulin therapy

Insulin is essential to a child with type 1 diabetes mellitus. Initially only a small dose is needed and this period, which is of variable duration, is known as the 'honeymoon period'.

The dose of insulin needs revision with growth. The commonly used regimen in a child is twice a day injection, either as a combination of soluble and isophane insulin, or the combined preparation. Two thirds of the dose is given in the morning and the rest at night. Mother should be advised to give the meal within 20 minutes of injecting the insulin. Parents should also be instructed about cleaning the site with water, and the technique of giving

the subcutaneous injection. The injecting sites are the upper arms, abdominal wall and the thighs. Parents and the child should be instructed to rotate the sites of injection, to prevent complications such as lipo-hypertrophy and lipo-atrophy. Revision of the dose is required depending on the glycaemic control, physical activity, growth of the child, and during an illness.

Panel 1. Important aspects of insulin therapy

- Dose is based on the weight of the child
- Relationship of insulin to meals
- Preparations available
- Storage
- Technique of administration
- Cleaning and rotating sites
- Complications of incorrect administration
- Revision of dose when required
- Insulin during an illness and in relation to physical activity

Monitoring glycaemic control

Short term control

If a glucometer is available parents are advised to do a blood glucose series for a few days before clinic visits to modify the insulin dose if required. Dose should not be changed based on one reading.

Long term control

HbA1C and fructosamine are indicators of control over the preceding 3 months and 6 weeks respectively.

Panel 2. Blood glucose targets

- Infants and children <6 years: 5-12 mmol/l
- Children 6 – 12 years: 4-10 mmol/l
- Adolescents and adults: 4-8 mmol/l
- Bedtime: 7-10 mmol/l
  <6 years: 7-12 mmol/l

Dietary management

The diet that is recommended for a child with diabetes is 'healthy eating' and should be the diet for the entire family. Education of parents regarding the principles of dietary management is a continuing process, which is initiated in hospital and reinforced during clinic visits.

Diet is based on the energy requirement of the child and is initially calculated for the weight at presentation and gradually increased to the mean of the current weight and 50th percentile weight. 55% of the daily calorie requirement should be from carbohydrates (CHO) and is calculated as portions (1 portion = 15g of CHO) with combinations of high and low glycaemic index foods. The portions are distributed according to the child's daily routine and given as 3 main meals and 3 snacks.

Panel 3. Diet in children with diabetes

- No restrictions, only modifications
- Based on the calorie requirement of the child
- Calculated as CHO portions and combinations of high and low glycaemic index foods
- Given as 3 main meals and 3 snacks, distributed according to the child's daily routine
- Modifications are needed with growth of the child
- This should be the family diet

Physical activity

Exercise is important for a child with diabetes and there should be no restriction in physical activity. Physical activity lowers blood glucose, which could manifest several hours after the activity and the severity of hypoglycaemia will depend on the level of activity. So parents and the child are advised to adjust the insulin dose according to the activity and to modify the diet.

Panel 4. Exercise and diabetes

- No restriction of any activity of the child
- Physical activity lowers blood glucose level
- Adjust insulin dose according to the activity and give additional snacks
- After prolonged physical activity – increase bedtime snack, check blood glucose at bedtime and at 3 am

Sick day management

Insulin should never be stopped during an illness. Dose could be modified depending on the food intake of the child. At least initially till the parents are confident and able, the child should be managed in hospital during an illness.

Screening for complications

This is recommended 5 years after diagnosis and annually thereafter. If the child was diagnosed around puberty, screening is done soon after.

Psychological support

This is an important part of management and should be offered to the entire family as and when required. The services of a diabetic nurse educator and a social worker are extremely important for continuing the education and supporting the family.

Further reading

1. De Silva KSH, Wickramasinghe VP, Gooneratne INA. Metabolic consequences of childhood obesity – a preliminary report. *The Ceylon Medical Journal* 2006; **51**: 105-9.
2. De Abrew WK. Information for people with diabetes, 2005. Department of Pharmacology, Faculty of Medicine, University of Colombo.
3. Diabetes education modules. International Diabetes Federation 2006.
4. Type 1 diabetes in children and young people. Information about NICE Clinical Guidelines 15, 2004.

Dr. Shamya de Silva, MBBS, DCH, MD, *Consultant Paediatrician and Senior Lecturer in Paediatrics, Faculty of Medicine, Colombo.*
Email: <paedcmb@gmail.com>

Conflicts of interest: none.

Atypical antipsychotics

Introduction

Chlorpromazine, the first clinically useful antipsychotic, was discovered in the 1950s. At first chlorpromazine was regarded as an antihistamine. When it was tested in patients with schizophrenia for its sedative effects, it was found to have unique antipsychotic properties. The mechanism of action was discovered only later. It was found that cholorpromazine and other antipsychotic agents caused "neurolepsis", a state of areflexia and rigidity in animals. New chemical compounds that had antipsychotic effects were tested by their ability to produce this effect in animals. These chemical entities are referred to as conventional antipsychotic.

In the late 60s and 70s it was discovered that they had the common property of blocking dopamine receptors in the brain. It was hypothesised that excess of dopamine in the mesolimbic system of the brain caused schizophrenia. They revolutionised the treatment of schizophrenia, and enabled a large number of long stay patients in mental asylums to return home. But there were side-effects. These drugs, in addition to blocking dopamine in the limbic system, also blocked dopamine receptors in the anterior pituitary leading to increased secretion of prolactin, and in the substantia nigra, causing extrapyramidal symptoms. The extra-pyramidal symptoms consisted of acute dystonia, parkinsonism, and the generally irreversible tardive dyskinesia.

The search went on for compounds, which did not block dopamine in other areas. The first such compound to be found was clozapine, which was soon followed by other compounds. These compounds did not cause neurolepsis in animals and were less likely to cause extrapyramidal side-effects in man. This group of compounds came to be known as **atypical antipsychotics**. The older group of antipsychotics are known as conventional or typical antipsychotics.

Clinical use of atypical antipsychotics

Their main clinical use is in the treatment of schizophrenia. The symptoms of schizophrenia are divided into two main groups. The positive symptoms consist of hallucinations, delusions: and negative symptoms include avolition, paucity of speech and thought, and amotivation. Both typical and atypical antipsychotics in general are effective in treating the positive symptoms of schizophrenia.

Though some studies have shown atypical antipsychotics to be more effective in treating negative symptoms, this effect is not consistent. Antipsychotics are useful in the treatment of psychotic symptoms in bipolar mood disorder, psychotic depression, and delusional disorders. They are also used in managing behavioural disturbances in delirium and dementia.

In schizophrenia the antipsychotics, typical and atypical, are used for four primary clinical purposes.

1. To manage acute positive psychotic symptoms
2. To induce remission from positive symptom episodes.
3. To maintain the clinical effect over a period of time (maintenance therapy).
4. To prevent relapses or new episodes of positive symptom expression (prophylactic therapy).

Clinical trials have not shown a significant difference in the above effects between conventional and atypical antipsychotics when given in equivalent doses. But the reduced incidence of extrapyramidal side-effects have made the atypical antipsychotics much more acceptable to patients. This is likely to improve patient compliance and reduce the likelihood of exacerbations caused by patients stopping their treatment early.

Types of atypical antipsychotics

There are at present eight atypical antipsychotics in use in the world. Sri Lanka has five, which will be described first.

Clozapine

This was the first clinically useful atypical antipsychotic. After initial use it was discontinued in a number of countries as it caused agranulocytosis in some patients. It came back into clinical use when it was found that clozapine was clearly superior to other antipsychotics in the treatment of resistant schizophrenia. It still remains the only psychotic clearly shown to be of value in the treatment of this condition. Because of the possibility of serious adverse effects it is not recommended for use in the initial treatment of schizophrenia.

Clozapine should be started at an initial dose of 25 mg daily, while monitoring the blood pressure (risk of syncope due to hypotension). The average therapeutic dose is 300 mg daily, although clinical experience suggests that, for smaller built Asians lower doses would suffice. The WBC is monitored weekly for the first 18 weeks and thereafter 4 weekly. If the leucocyte count drops below 3000/mm^3 or the absolute neutrophil count below 1500/mm^3 clozapine should be stopped.

Clozapine is known to cause mycarditis and cardiomyopathy. A cardiovascular examination and an ECG are therefore advisable before starting therapy. Clozapine is also more likely to cause seizures compared to other antipsychotics.

Risperidone

This antipsychotic has a chemical structure different from that of other antipsychotics. Its distinctive properties have been attributed to its antagonism of both serotonin and dopamine receptors. Risperidone, unlike most other atypical antipsychotics, causes hyperprolactinaemia leading to menstrual irregularities, amenorrhoea, and galactorrhoea. These side-effects might make it unacceptable to women who wish to get pregnant.

Olanzapine

Olanzapine is known to cause orthostatic hypotension, and especially in the elderly it is advisable to start on a dose of 5 mg daily. There have been reports of aggravation of diabetes mellitus with olanzapine. The clinician should bear this in mind when treating patients with diabetes. Olanzapine is particularly associated with weight gain, which makes it unacceptable to some patients.

Quetiapine

Approved for use by the FDA in 1997, quetiapine has some advantages over the previous atypical antipsychotics. It does not cause significant elevation of prolactin, and is less likely to cause sexual dysfunction. It is also less likely to cause weight gain and extrapyramidal side-effects.

Aripiprazole

This is a newer atypical antipsychotic. Its unique action is thought to be due to its partial antagonistic effect on

D_2 receptors. It is postulated that the negative symptoms of schizophrenia are due to reduced dopamine activity in the frontal lobes and that the positive symptoms are due to increased dopamine activity in the mesolimbic system. By its partial antagonism of dopamine receptors aripiprazole may increase dopamine activity in the frontal lobe, thereby relieving the negative symptoms of schizophrenia. Aripiprazole may well be the first antipsychotic that can reduce negative symptoms of schizophrenia.

The following atypical antipsychotics are not available in Sri Lanka.

Amisulpride

It is a dual 'dopamine blocker'. At low doses (50 to 200 mg) it blocks presynaptic dopamine autoreceptors facilitating dopamine release and has a mood elevating effect. At higher doses (400 to 1200 mg) it blocks D_2 receptors reducing dopamine transmission and has an antipsychotic effect. In an important metanalysis by Davis (2003) its effect size (0.29) was second only to that of clozapine, the most effective antipsychotic. Yet it has never been marketed aggressively unlike some other atypicals such as olanzapine, probably because it is off-patent, with little profit for the pharma-ceutical industry. It has a lower propensity for weight gain and extrapyramidal side-effects. Adverse effects of amisulpride include insomnia, anxiety, agitation, drowsiness, gastrointestinal disorders, dry mouth, hyperprolactinaemia, and occasionally, bradycardia.

Praliperidone

One of the latest antipsychotics it is an active metabolite of risperidone. The oral form is a sustained release formulation and may require less dose titration. It has lower peak dose plasma levels, and thus less extra-pyramidal side-effects and less sedation, compared to risperidone. But it has much the same risk for weight gain, diabetes and hyperprolactinaemia.

Ziprasidone

Ziprasidone has a novel chemical structure and pharmacological properties. It is highly effective against positive symptoms of schizophrenia and also improves negative symptoms. The dose is important for its efficacy. The dose should be increased rapidly to middle or top of the dose range, and given twice daily with food to increase absorption and maximise effectiveness. It has a low incidence of extrapyramidal side-effects and prolactin elevation. It causes minimal weight gain, with little association with dyslipidaemia. Early concerns about dangerous QTc prolongation now appear to have been unjustified. It is an excellent antipsychotic but is not available in the UK.

Panel 1. Dose range of atypical antipsychotics

Antipsychotic	Minimum dose	Maximum dose (UK licensed)
Aripiprazole	10 mg	30 mg
Clozapine	150 mg	900 mg
Olanzapine	10 mg	20 mg
Quetiapine	150 mg	800 mg
Risperidone	2 mg	16 mg
Ziprasidone	80 mg	160 mg

Using atypical antipsychotics

The National Institute for Clinical Excellence (NICE) of the UK has published the following guidelines for the use of atypical antipsychotics.

A. The atypical antipsychotics should be considered for 1. treating newly diagnosed schizophrenia 2. managing an acute schizophrenic episode when discussion with the patient is not possible 3. a patient who is suffering unacceptable side-effects with a conventional antipsychotic 4. a patient in relapse whose symptoms were previously inadequately controlled.

B. Changing to an atypical antipsychotic is not necessary if a conventional antipsychotic is adequately controlling symptoms and there are no unacceptable side-effects.

C. Clozapine should be considered if schizophrenia is inadequately controlled despite the sequential use of two or more antipsychotics (one of which should be an atypical antipsychotic) each for at least 6 to 8 weeks.

Metabolic side-effects

Atypical antipsychotics have been available for over 10 years. Only recently it has become evident that some of these drugs are associated with significant metabolic risks. Weight gain, obesity, and more recently, increased risk of hyperlipidaemia, diabetes, accelerated cardiovascular disease have been linked to certain drugs in this class. Partly these effects are due to increased appetite but receptor mediation also probably plays a role.

Panel 2. Atypical antipsychotics and risk of weight gain

Antipsychotic	Risk of weight gain
Clozapine	+++
Olanzapine	+++
Risperidone	++
Quetiapine	++
Ziprasidone	+/-
Aripiprazole	+/-

In spite of these potential problems the atypical antipsychotics have greatly improved the treatment of schizophrenia. The use of atypical antipsychotics has been restricted in the West due to its relatively high cost. In Sri Lanka these drugs are available relatively cheaply from India, and we may be less restrictive in their use. The Ministry of Health should make these more widely available in the state health sector.

Further reading

1. Stahl SM. Essential Psychopharmacology, Third Edition, Cambridge University Press; 2008: 327- 451.
2. British National Formulary, No 57; British Medical Association, Royal Pharmaceutical Society of Great Britain; March 2009: 197-202.
3. The Maudsley Prescribing Guidelines, 9th Edition, 2008: 13-28.

Dr. Raveen Hanwella, MBBS, MD, MRCPsych, *Consultant Psychiatrist and Senior Lecturer in Psychiatry, Department of Psychological Medicine, Faculty of Medicine, Colombo.*
Email: <raveenhanwella@yahoo.co.uk>

Conflicts of interest: the author has received educational grants from pharmaceutical companies.

Restless legs syndrome

Summary

Restless legs syndrome is common. While many patients are simply inconvenienced, others suffer greatly from wakefulness and disturbed sleep. The condition is readily recognised by history and examination and perhaps simple investigations. Secondary causes should be excluded. Mild symptoms can be managed without drugs, but severe symptoms may require a dopamine agonist. Treatment is usually effective but may present some practical difficulties.

Key words: dopamine agonists, opioids, pramipexole, ropinirole.

(Aust Prescr 2008,31:90-3)

Introduction

About 5-15% of the population are affected by restless legs syndrome.[1] Probably the earliest description was written in 1683 in 'Two discourses concerning the soul of brutes':

> ... whilst they would indulge in sleep, in their beds, immediately follow leapings up of the tendons in their arms and legs, with cramps, and such unquietness and flying about of their members, that the sick can no more sleep, than those on the rack.[2]

This captures the elements of restless legs syndrome: sensory discomfort ('cramps'), motor restlessness ('unquietness'), the associated involuntary movements during sleep and wakefulness ('flying about of their members'), aggravation by night and rest ('in their beds'), sleep disruption, and the tortured condition of the worst affected ('on the rack').

Restless legs syndrome can begin at any age. Earlier, slower onset suggests hereditary restless legs syndrome and later, abrupt onset, secondary restless legs syndrome. At first exacerbations and remissions occur, but then the tendency is for a static or chronic progressive course. Although some people have severe symptoms, most people do not require drug treatment.

Diagnosis and classification

The clinical evaluation of restless legs syndrome, particularly the patient's history, is very important.The diagnosis is based on criteria proposed at a consensus conference held at the National Institutes of Health in the USA (see box).[1] The condition is classified as 'idiopathic' or secondary to several other conditions (Table 1).

Essential diagnostic criteria

Typically, patients complain of limb (usually leg) discomfort at rest, an urge to move the affected part, and unpleasant sensory symptoms. They often find it hard to describe the sensations, or say 'creeping, crawling, itching, burning, searing, tugging, pulling, drawing, aching, hot and cold, electric current-like, restless or painful'. These sensations are felt deep in muscle or bone, seldom in a joint. The whole limb or part of it may be involved, even unilaterally. In about half the cases, arms and legs are affected, but sole involvement of the arms is unommon. Occasionally, the sensory symptoms are absent.

Usually, the symptoms begin after the patient has been lying or sitting quietly. Symptoms only on sitting are very uncommon. The more mentally rested and physically quiet the patient is, the more intense the symptoms. They can last for a few minutes or an hour.

Voluntary movement, not necessarily of the affected parts, promptly but only temporarily relieves the symptoms. A characteristic history is that the patient moves about in their chair or bed, gets up and paces about, stretches the limbs or rubs the legs to get relief. Placing the limbs on a cold or hot surface sometimes helps.

The worst times are from the evening to the early hours of the morning, whether or not the patient is asleep. This circadian pattern may be lost in severe cases and it is modified by shift work, medication and sleep disorders.

Diagnostic criteria for restless legs syndrome[1]

Essential criteria

1. An urge to move the legs (and occasionally the arms or other body parts) usually, but not always, accompanied by uncomfortable or unpleasant sensations
2. The symptoms begin or worsen during periods of rest or inactivity such as lying or sitting
3. Movement such as walking or stretching partially or totally relieves the symptoms at least as long as the activity continues
4. A circadian pattern: the symptoms are worse or only present in the evening or at night and this diurnal variation must have once been present if the symptoms are now so severe as to make diurnal variation unnoticeable

Supportive of the diagnosis

1. Family history
2. Response to dopaminergic therapy
3. Periodic limb movements during wakefulness or sleep

Supportive clinical features

Over 50% of patients have a family history of restless legs syndrome. The pattern is consistent with an autosomal dominant mode of inheritance.

In 80% of patients, repetitive flexing movements of the legs (occasionally the arms), and dorsiflexion and fanning of the toes, for 0.5-5 seconds every 5-90 seconds, occur during sleep or wakefulness. While common, these movements are not required for the diagnosis of restless legs syndrome, nor are they specific to the condition, occurring normally and in a number of other conditions.

Associated features

Over 90% of patients have insomnia – usually trouble initiating or maintaining sleep.The neurological examination is usually normal although there may be signs of neuropathy in some secondary cases. There is an association between restless legs syndrome and cardiovascular disease.[3] Clinical examination is mainly directed at identifying causes of secondary restless legs syndrome (Table 1).

Table 1

Classification of restless legs syndrome

Primary	Secondary
'Idiopathic'	Iron deficiency
	Pregnancy, especially in third trimester, resolving with delivery
	Uraemia
	Peripheral neuropathies generally, and specifically Charcot-Marie-Tooth type 2 and familial amyloid neuropathy
	Diabetes
	Rheumatoid arthritis
	Vitamin B_{12}, folate deficiency
	Spinocerebellar ataxia, especially type 3
	?Parkinson's disease
	Drugs: antiemetics, e.g. metoclopramide; some anticonvulsants, e.g. phenytoin; antipsychotic agents, e.g. phenothiazines and haloperidol; occasionally tricyclic antidepressants, selective serotonin reuptake serotonin inhibitors, lithium

Investigations

Laboratory testing is fairly limited unless a secondary cause is suspected from the history or examination. Measuring iron and ferritin is particularly important as low stores may precipitate and aggravate restless legs syndrome. Recently, measures of ferritin in the cerebro-spinal fluid and MRI scans showing reduced iron in the red nucleus and striatum suggest that iron stores in the brain are reduced.[4]

Nerve conduction studies are indicated if the clinical evaluation suggests a neuropathy. They are of doubtful use otherwise, particularly if there is a family history.

Sleep studies for the formal evaluation of sleep quality or periodic limb movements during sleep are neither generally feasible or usually required.They may be considered if excessive daytime somnolence suggests significant sleep disruption.

Differential diagnosis

Peripheral arterial disease, arthritis and bursitis are easily distinguished by examination. Most painful conditions are not instantly ameliorated by activity.

Restless legs syndrome should be distinguished from akathisia.* The clinical setting may help, for example exposure to an offending drug (such as an antipsychotic or metoclopramide) in akathisia. Patients with restless legs syndrome emphasise the provocative nature of rest and sleep, identify the sensory disturbance as the cause of motor restlessness and have greater relief from activity. On the other hand, repetitive stereotyped movements, like body rocking, are more likely in akathisia, in which such overt motor behaviour is usually evident during the examination. The absence of symptoms while lying down generally excludes a diagnosis of restless legs syndrome.

The association with Parkinson's disease is not established by well-designed studies, but both conditions respond to dopaminergic drugs and are associated with periodic limb movements during sleep.The pathology of Parkinson's disease, however, is quite different.

Treatment

Any underlying causes should be identified and treated. Mild symptoms may respond to good sleep hygiene (Table 2) or simple analgesics. More severe symptoms may need to be managed with dopaminergic drugs, opioids or benzodiazepines. Most trials have used levodopa and dopamine agonists, but other drugs such as amantadine, selegiline and anticonvulsants also have reported efficacy. Initially at least, 90% of patients report relief with levodopa or dopamine agonists. Generally the doses are much smaller than those used in Parkinson's disease.

Opioids or benzodiazepines have a role in drug treatment of occasional symptoms as long as the patient and doctor understand the potential for dependence and withdrawal and restrict their use to only a few days in the month. Of the benzodiazepines, most published experience concerns treatment with clonazepam. This has a modest benefit, but may also be complicated by sedation and confusion. Opioids may be useful when dopaminergic drugs are poorly tolerated or are unhelpful. The advantages of opioids are long half-life and the absence of augmentation as an adverse effect. Another alternative is gabapentin, especially when pain is prominent. The class of drugs shown to be ineffective are anti-cholinergics; antidepressants with anticholinergic effects may worsen restless legs syndrome.

* Akathisia: a feeling of inner restlessness which makes the person unable to sit still.

Table 2

Good sleep hygiene

Sleep/wake activity regulation	Establish regular sleep times
	Avoid oversleeping
	Avoid excessive napping (limit to afternoon 'powernap' of 10-15 minutes)
	Exercise regularly (at least six hours before bedtime)
Sleep setting and influences	Avoid bright light exposure in late evening or night, but bright light after rising may be helpful
	Avoid heavy meals within three hours of bedtime
	Sleep in a quiet, dark room (remove TV, stereo)
	Use a suitable mattress and pillow for comfort and support
	Reserve bedroom for sleep and intimacy
	Avoid alerting and stressful ruminations before bedtime (doing jigsaws may help)
	Avoid caffeine after lunch
	Reduce excessive alcohol intake
	Avoid tobacco, especially after dinner
Sleep promoting adjuvants	Have a light snack or warm bath before bed
	Engage in quiet activities before sleep, eg. reading

As the condition often fluctuates over time, the mildly affected patient may be able to use medication intermittently. Continuous treatment should be reserved for more severely affected individuals. Generally, idiopathic restless legs syndrome does not resolve.

Dopamine agonists

Low-dose dopamine agonists are largely replacing levodopa as first-line treatment for restless legs syndrome because of ease of management and better efficacy. cabergoline has the advantage of a very long half-life and had superior efficacy to levodopa in the first large randomised controlled trial comparing two dopaminergic therapies in restless legs syndrome.[5] Of the newer non-ergot derived dopamine agonists, ropinirole has been the most extensively studied[6], followed by pramipexole.[7] If there are significant daytime symptoms, patients may need multiple doses or long-acting preparations. As a general rule, doses should start low and be increased gradually to avoid adverse effects. It is important to keep doses low as there is no extra benefit from the higher doses used in Parkinson's disease, and because of the risk of augmentation with higher doses.

Adverse effects

Several problems may be encountered usually within 3-4 months of starting a dopaminergic drug. The phenomenon of augmentation complicates treatment in up to 80% of patients, as early as 3-4 weeks into treatment. In augmentation, the symptoms are shifted to an earlier time in the day, may be more severe and more easily provoked and may spread to previously uninvolved limbs. Pain and sleeplessness cause severe anxiety and so augmentation is important to recognise. Raising the dose aggravates augmentation, but it resolves on withdrawal of the drug. Risk factors for augmentation are taking the dose well before symptom onset, and doses of levodopa above 200 mg per day. It is primarily a problem with levodopa, but has also been reported with pergolide. So far, it seems that augmentation is less of a problem with cabergoline and non-ergot dopamine agonists. If augmentation occurs, it is best to switch to or between dopamine agonists, or temporarily use opioids while the dose of the dopaminergic drug is lowered.

Another problem is rebound, in which the symptoms of restless legs syndrome reappear after the drug has worn

off. This is similar to 'wearing off' in Parkinson's disease and manifests as early morning or late night symptoms. Rebound is related to the half-life of the drug, so it is best to use a long-acting preparation, multiple dosing or switc to cabergoline.

Concerns have arisen over the use of ergot-derived dopamine agonists (such as cabergoline and pergolide) in the treatment of Parkinson's disease because of the serious complication of restrictive cardiac valvulopathy.[8] The risk could be smaller with bromocriptine and with the lower doses used in restless legs syndrome, but good studies are lacking. Great caution should therefore be used when prescribing cabergoline or pergolide.

If they are necessary, regular (six-monthly) echo-cardiography is recommended, although we still do not know if the valvulopathy is reversible. The non-ergot derived dopamine agonists (such as ropinirole and pramipexole) have not yet been implicated in valvulo-pathy. There have been no direct comparative studies between cabergoline, pramipexole and ropinirole, therefore no claim for greater efficacy can be made for any of these drugs.

Common adverse effects of dopamine agonists, particularly at the start of treatment, are nausea and dizziness (due to postural hypotension). Impulse control disorders including pathological gambling and hypersexuality are increasingly being recognised. Another concern is pathological daytime somnolence occurring as 'sleep attacks' which may cause motor vehicle accidents. While these adverse effects seem dose related, they may occur with the relatively low doses used in restless legs syndrome, so awareness and caution are necessary.

Opioid treatment may be complicated by sedation and constipation. It has the potential for abuse, dependency and withdrawal, so occasional use is preferable. Caution should be exercised in prolonged treatment.

Conclusion

Restless legs syndrome is a common but under-recognised disorder. For patients with mild symptoms, no drug treatment may be necessary. For patients with severe symptoms, dopamine agonists are the first-line treatment when a drug is needed. Some patients can be managed with intermittent therapy.

References

1. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003; 4:101-19.
2. WillisT. The practice of physick. Two discourses concerning the soul of brutes. Samuel Pordage (trans. 1683). London: T Dring, C Harper and J Leigh; 1684.
3. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurology 2008;70:35-42.
4. Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Ondo WG, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003;61:304-9.
5. Trenkwalder C, Benes H, Grote L, Happe S, Hogl B, Mathis J, et al; CALDIR study group. Cabergoline compared to levoclopa in the treatment of patients with severe restless legs syndrome: results from a multi-center, randomized, active controlled trial. Mov Disord 2007;22:696-703.
6. Trenkwalder C. The weight of evidence for ropinirole in restless legs syndrome. Eur J Neurol 2006;13 Suppl 3:21-30.
7. McCormack PL, Siddiqui MA. Pramipexole: in restless legs syndrome. CNS Drugs 2007;21:429-37; discussion 438-40.
8. Antonini A, Poewe W. Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson's disease. Lancet Neurol 2007;6:826-9.

Further reading

Headrick S, Adsett M, Lander C. Medicinal mishap: Cabergoline-induced valvulopathy. Aust Prescr 2008;31:21.

Conflict of interest: none declared.

Dominic Thyagarajan, *Associate Professor and Head of Neurology, Flinders Medical Centre, Adelaide*

This article is reproduced from the *Australian Prescriber* 2008; **31**: 90-3, by prior arrangement, courtesy of *Australian Prescriber*.

Current information about drug registration

New chemical entities registered

Generic name	Brand name	Dosage form	Manufacturer	Importer	Therapeutic class / use(s)
Alteplase	Actilyse	Injection – 20 mg, 50 mg	Boehringer Ing., Germany	Hemas	Fibrinolytic
Cadexomer iodine	Iodosorb	Ointment – 0.9%	Perstop, Sweden	CIC	Chronic wounds
Daptomycin	Cubicin	Injection – 500 mg	Hospira, USA	SJ Enterprises	Lipopeptide antibacterial
Fondaparinux sodium	Arixtra	Injection – 2.5 mg/0.5 ml (pre-filled syringe)	Glaxo, France	GSK	Anticoagulant
Human papillomavirus vaccine [Types 16, 18]	Cervarix	Injection – 20 mcg/0.5ml (pre-filled syringe)	GSK, Belgium	GSK	Cervical cancer
Lanthanum carbonate	Fosbait	Tablet – 250 mg	Panacea, India	Robert Hall	Hyperphosphataemia
Levocetirizine	Verizet	Tablet – 5 mg	Sun, India	Harcourts	Antihistamine
Retapamulin	Altargo	Ointment – 1%.	Glaxo, UK	GSK	Topical antibiotic
Sunitinib	Sutent	Capsule – 12.5 mg, 25 mg, 50 mg	Pfizer, Italy	Hemas	Antineoplastic
Tenecteplase	Metalyse	Injection – 40 mg, 50 mg	Boehringer Ing., Germany	Hemas	Fibrinolytic
Tigecycline	Tygacil	Injection – 50 mg	Wyeth, USA	Edna	Tetracycline antibiotic
Zanamivir	Relenzal	Inhalation – 5 mg/dose	Glaxo, France	GSK	Influenza

For further information please contact **Professor Gita Fernando,** *Department of Pharmacology, Faculty of Medical Sciences, University of Sri Jayewardenepura.*

Printed by Ananda Press, Colombo 13.

ISSN 1391-0736