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A **NEW** SNRI THERAPY FOR DEPRESSION

A New Gateway of Treatment

A New Way of Life

Predictable...

- Metabolism independent of CYP2D6 pathway in the liver¹⁻³
- Low potential for CYP2D6-mediated drug-drug interaction⁴

Reliable...

- Discontinuation rate due to adverse events comparable to placebo⁴

Convenient...

- One simple 50 mg dose⁴

PRISTIQ® ABBREVIATED PACKAGE INSERT. TRADE NAME: PRISTIQ®. PRESENTATION: Pristiq is formulated as an extended-release tablet which contains 76 mg of desvenlafaxine succinate equivalent to 50 mg of desvenlafaxine. Light pink, square (pyramid-one side) tablet debossed with "W" (over) "50" on one side. **INDICATIONS:** Pristiq is indicated for the treatment of major depressive disorder (MDD). **DOSAGE & ADMINISTRATION:** The recommended dose for Pristiq is 50 mg once at approximately the same time daily, with or without food. Pregnant women during the third trimester, child & adolescent must balance the potential risks with the clinical need; No dosage adjustment in patient with mild renal impairment but the recommended dose in patients with moderate renal impairment is 50 mg per day; The recommended dose in patients with severe renal impairment or end-stage renal disease (ESRD) is 50 mg every other day. Supplemental doses should not be given to patients after dialysis; No adjustment of the starting dosage for patient with hepatic impairment; No dosage adjustment is required solely on the elderly patients but the possibility of reduced renal clearance of Pristiq should be considered when determining the dose. **CONTRAINDICATIONS:** Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation. Must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days. **WARNINGS & PRECAUTIONS:** All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Not approved for use in treating bipolar depression; Serotonin syndrome or NMS-like reactions; Activation of mania/hypomania; Elevated blood pressure & abnormal bleeding; Serum cholesterol & triglyceride elevation; Narrow-angle glaucoma; Renal impairment; Seizure; Hyponatremia; Interstitial lung disease & Eosinophilic pneumonia; New symptoms and serious discontinuation symptoms were reported in discontinuation of treatment; Caution is advised to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders; Co-administration of drugs containing desvenlafaxine & venlafaxine is not recommended. **SIDE EFFECTS:** Most commonly observed adverse reactions in short-term fixed-dose studies were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. Hypertensitivity effects on blood pressure, abnormal bleeding, myasthenia, hypomania & mania, serum cholesterol & triglyceride elevation, and seizure were also reported. **INTERACTIONS:** Risk in combination with other CNS-active drugs has not been systematically evaluated and caution is advised; MAOI; Serotonergic drugs; Drugs that interfere with hemostasis; Not increase the impairment of mental and motor skills caused by ethanol but advised to avoid alcohol consumption; Concomitant use with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq; inhibitors of other CYP enzymes are not expected to have significant impact on the pharmacokinetic profile of Pristiq; Minimal inhibitory effect of desvenlafaxine on CYP2D6; Not inhibit or induce the CYP3A4 isozyme; Not inhibit CYP1A2, 2A6, 2C8, 2C9 & 2C19 isozymes & not expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes; Not a substrate or an inhibitor for the P-glycoprotein transporter; No clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **PREGNANCY AND LACTATION:** Pregnancy Category C. Carefully consider the potential risks and benefits of treatment when treating a pregnant woman during the third trimester, labor and delivery. Excreted in human milk; breastfeed if the expected benefits outweigh any possible risk. **DRUG ABUSE AND DEPENDENCE:** Not systematically studied in preclinical/clinical studies for its potential for abuse. Physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Pristiq. Limited clinical experience with desvenlafaxine succinate overdose in humans. **Reference:** W10529C005-HK, 04/09. **Date of preparation:** MAY2010. **Identifier number:** PRIS0610. **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**



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 4. Pristiq® Approved Product Information.
 Further information is available upon request.



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Chronic medical conditions, like many neurological and psychiatric disorders, cause significant and persistent suffering to patients in terms of disability-adjusted life years (DALYs) and personal distress. As treatment may not be curative, there is an unmet need for long-term maintenance treatment to control symptoms, and prevent relapse and recurrence.

For example, unipolar depression has been reported by the World Health Organization to be the third leading contributor to the global burden of disease in terms of DALYs in 2004, and has been projected to take first place by the year 2030, even higher than that for ischaemic heart disease. The suicide rate of patients with unipolar depression can reach 15%. In addition, unipolar depression is associated with reduced productivity, poor work performance and absenteeism, and can be translated into large direct and indirect costs to the global economy. Therefore, proportionate resources are urgently needed to proactively prevent or manage unipolar depression, and to minimise the economic costs, based on the rationale of “investing to save”.

This July issue includes articles on neurology, psychiatry, geriatrics and liver disease, authored by experienced specialists, to provide readers with updates on medical advances in these fields.



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Pictorial Medical History (3)

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Asclepius was the ancient Greek god of medicine. He was one among a family pantheon of doctors; his father, Apollo, was a healing god and his daughters included Hygieia (personifying hygiene), Iaso (associated with recuperation) and Panacea (embodying all-cure medicine). His two sons, Podaleirius, a physician, and Machaon, a surgeon, were respected army doctors in the Trojan War. The great poet Homer referred to Asclepius in the Iliad as “the blameless physician”.

Asclepius is often depicted as a mature bearded man with a bare chest, holding a rough-hewn staff entwined by a sacred snake; this snake-staff is called the Asclepian.



Asclepius, son of Apollo and Greek god of medicine, holding the Asclepian

**Ny Carlsberg Glyptotek
(sculpture museum)
Copenhagen, Denmark**

Novel Pharmacological Option for Major Depressive Disorder



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Key words:

Depression (抑鬱症), serotonin and norepinephrine reuptake inhibitors (血清素/去甲腎上腺素再攝取抑制劑), desvenlafaxine (地文拉法辛)

Introduction

Depression is a common mental disorder. In 1990, the World Health Organization (WHO) identified depression as the fourth leading contributor to the global burden of disease for all ages, in terms of disability-adjusted life years, and it is projected to become the second then leading cause of global disease burden by 2020 and 2030, respectively.¹⁻⁴ A large-scale community survey on mental health, revealed that mood disorder is one of the most common conditions in Hong Kong, especially among females.⁵

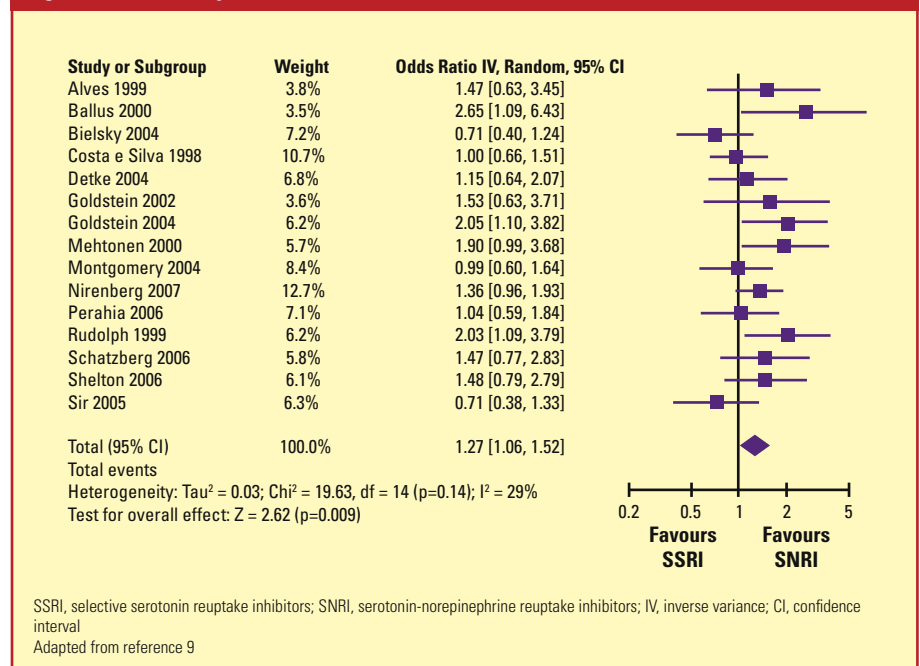
Major clinical guidelines for the treatment of major depressive disorder (MDD), including the 2009 National Institute for Health and Clinical Excellence (NICE) clinical guideline, 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guideline and 2010 American Psychiatric Association practice guideline for treatment of

major depressive disorder, share striking similarities. These guidelines focus on the treatment aim of achieving remission using a stepped-care approach, based on disease severity, with pharmacological treatment algorithms. They recommend the combination of pharmacological and psychological treatment modalities to optimise treatment outcomes, and emphasize the importance of addressing inadequate response and preventing relapse.⁶⁻⁸

Therapeutic options

Therapeutic options for depression include medication, psychotherapy and electroconvulsive therapy. The 2009 NICE clinical guideline for treatment of MDD, recommends selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine and dopamine reuptake inhibitor (NDRI), noradrenergic and

Figure 1. Meta-analysis of head-to-head trials between SSRIs and SNRIs



selective serotonergic agonist (NaSSA) and reversible inhibitor of monoamine oxidase inhibitor (RIMA) as first-line antidepressant treatments.⁶ A meta-analysis of head-to-head trials between SSRIs and SNRIs revealed a 5.7% difference in remission rates in favour of SNRIs.⁹ (Figure 1)

A new pharmacological option for MDD – desvenlafaxine

About 56% of venlafaxine is metabolised by the cytochrome P450 2D6 (CYP2D6) isoenzyme to become the major active metabolite, o-desmethylvenlafaxine or desvenlafaxine, which is thought to be largely responsible for the pharmacologic activity of venlafaxine. Desvenlafaxine (Pristiq, Pfizer) is formulated as a succinate salt. Data from an open-label, randomised four-period, and crossover study conducted in 24 healthy subjects suggested that, desvenlafaxine represents 70% of the overall concentration in the majority of subjects at steady state. In vitro studies have also demonstrated that desvenlafaxine is equipotent to venlafaxine.^{10,15}

“The pharmacological effect of desvenlafaxine, being an active metabolite, is independent of hepatic metabolism through the CYP2D6 isoenzyme pathway”

Desvenlafaxine is different from venlafaxine

Desvenlafaxine is an SNRI and inhibits the reuptake of both serotonin and

Characteristic	Desvenlafaxine	Venlafaxine
Absorption		
Oral bioavailability	~80%	45%
Half-life (t _{1/2})	~11 hours	~5 hours
T _{max}	~7.5 hours	~5.5 hours
Coadministration with food	Minimal effects	Minimal effects
Distribution		
Protein binding	~30%	27%
Metabolism		
Main metabolism route	Glucuronidation	CYP2D6
CYP3A4	Minor metabolic path	Minor metabolic path
CYP2D6	Not involved; minimal inhibition	Major metabolic path; minimal inhibition
Metabolites	3	6
PGP transport system	Not substrate or inhibitor	Not substrate or inhibitor
Elimination	45% unchanged	5% unchanged

T_{max}: time to maximum concentration; CYP3A4, cytochrome P450 3A4; CYP2D6, cytochrome P450 2D6; PGP, p-glycoprotein
Adapted from references 12 and 13

norepinephrine. It has a lower serotonin:norepinephrine selectivity ratio of 1:14 compared with 1:30 for venlafaxine,¹⁶ as well as higher oral bioavailability and longer half-life. The pharmacological effect of desvenlafaxine, being an active metabolite, is independent of hepatic metabolism through the CYP2D6 isoenzyme pathway. Approximately 45% is excreted unchanged renally at 72 hours after oral administration.^{12,13} (Table 1)

Low potential of drug-drug interactions with desvenlafaxine

Many medications, including cardiovascular medications, prescription analgesics, antidepressants, antipsychotics, antifungal agents, HIV protease inhibitors, cough suppressants and antihistamines, are metabolised by CYP2D6 isoenzymes.^{17,18} Also, the majority of patients treated for MDD routinely receive three or more medications to manage a variety of comorbid conditions.¹⁹ Due to the different genetic polymorphisms of the CYP2D6 isoenzyme, individuals lacking this gene are considered poor metabolisers while other polymorphisms may cause individuals to be ultra-rapid metabolisers.²⁰ These phenotypic variations affect the plasma con-

Minimal or low potential	<ul style="list-style-type: none"> • Desvenlafaxine • Citalopram • Escitalopram • Venlafaxine • Mirtazapine
Moderate potential	<ul style="list-style-type: none"> • Agomelatine • Bupropion • Duloxetine
Higher potential	<ul style="list-style-type: none"> • Fluoxetine • Fluvoxamine • Moclobemide • Paroxetine • Selegiline • Sertraline

Adapted from reference 7

centration, bioavailability and efficacy of medications. In addition, concomitant medications may compete for CYP2D6 isoenzyme metabolism and further affect the therapeutic efficacy of the medications administered. As desvenlafaxine is an active metabolite, its plasma concentration is unaffected by phenotypic variations in CYP2D6 isoenzyme,²¹ while drugs that inhibit CYP2D6 isoenzyme are not expected to significantly impact on the pharmacokinetics of desvenlafaxine. Thus, according to the 2009 CANMAT guideline, desvenlafaxine has a better safety profile in terms of lower potential for drug-drug interactions compared with other antidepressants.⁷ (Table 2)

Weight gain and sexual dysfunction

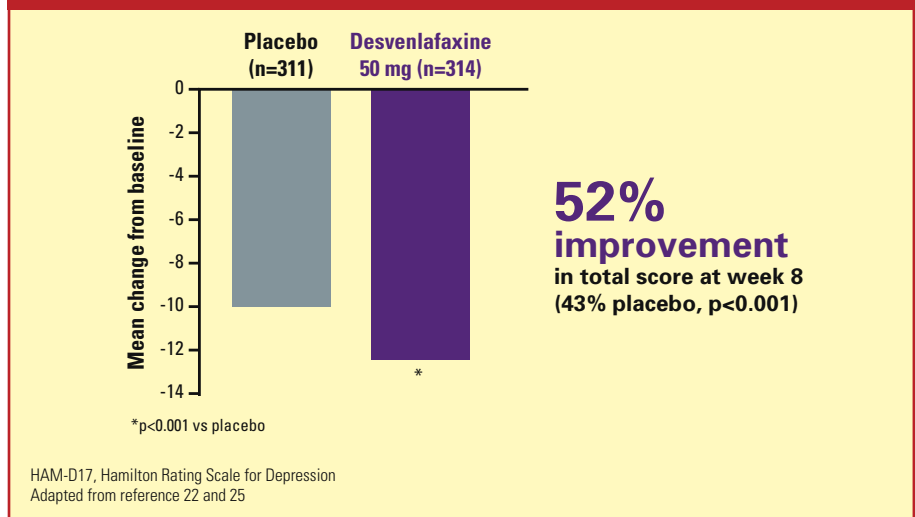
In one 6-month study, the rates of clinically significant weight gain ($\geq 7\%$) with desvenlafaxine 200–400 mg per day were comparable to those of placebo (13% vs. 7%, $p=0.083$).²² A double-blind extension study for patients who responded to desvenlafaxine in a 12-week open-label phase, showed no significant difference in the proportion of patients with clinically significant weight gain versus placebo between the open-label baseline and double-blind endpoint (19% vs. 12%, $p=0.064$).^{22,23} In two separate 8-week studies, no significant mean weight gain was reported with desvenlafaxine 50 mg per day compared with placebo (-0.44 kg vs. 0.05 kg, $p=0.001$).²⁴ No significant mean weight change between patients receiving desvenlafaxine 50 mg per day and placebo were reported at 6 months.²⁵

Comparable mean changes from baseline at weeks 4, 8 and 12 in terms of sexual dysfunction, as measured by the Arizona Sexual Experience Scale, were observed in both the desvenlafaxine and placebo arms for both genders in a 12-week clinical study.²²

Discontinuation rate due to adverse events and post-discontinuation events

Pooled data from nine double-blind, randomised, placebo-controlled, fixed- or flexible-dose, 8-week trials of 50, 100, 200 and 400 mg per day of desvenlafaxine in adults aged 18 years or older with MDD, showed that the discontinuation rate with desvenlafaxine treatment was comparable to that of placebo.²⁶ Common adverse reactions observed in patients taking desvenlafaxine 50 mg versus placebo in 8-week studies (defined as incidence $\geq 5\%$ and ≥ 2 times the rate of placebo) included nausea, dizziness, hyperhidrosis, constipation and decreased appetite. Nausea was generally mild to moderate and its prevalence decreased to placebo-like levels within

Figure 2. Change in total HAM-D17 score^{22,26}



“The data showed that the probability of relapse with desvenlafaxine 50 mg per day was 14.3% versus 30.2% with placebo 6 months later”

1 week. At the recommended dose of 50 mg, 1% of patients discontinued desvenlafaxine resulting from nausea.^{22,24}

In another study, the rate of post-discontinuation events was comparable to that of placebo (up to 47% for desvenlafaxine 50 mg per day vs. 27% for placebo) as evaluated by Discontinuation-Emergent Signs and Symptoms scores, which measure the presence of symptoms and not their severity.²² The common discontinuation symptoms experienced with desvenlafaxine 50 mg were nausea (8.8% vs. 2.4% for placebo), dizziness (11.7% vs. 1.7% for placebo), diarrhoea (5.0% vs. 1.7% for placebo), and irritability (5.0% vs. 1.7% for placebo).²²

Efficacy in clinical and functional improvements

Analysis of pooled data from 2 double-blind, randomised, placebo-controlled, fixed-dose, 8-week trials conducted in adults aged 18 years or older with MDD, showed that desvenlafaxine 50 mg per day was associated with a 52% improvement, compared with 43% for placebo, as measured by the Hamilton

Rating Scale for Depression total score.²⁶ (Figure 2)

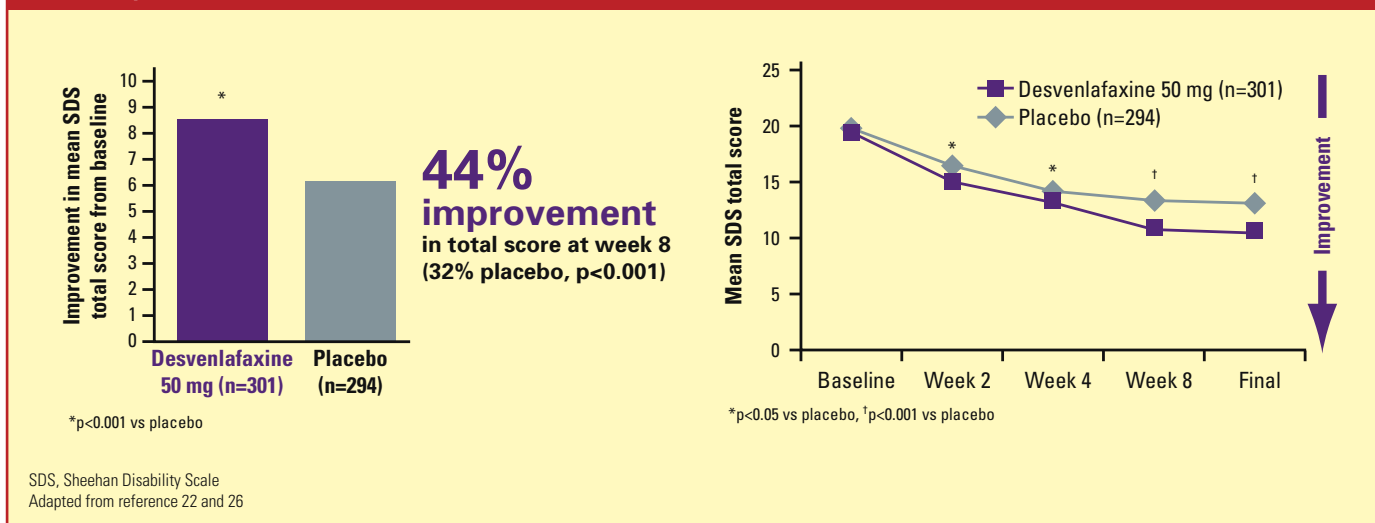
In addition, as assessed with the Sheehan Disability Scale in three domains (work, social life/leisure activities, family life/home responsibilities), patients receiving desvenlafaxine showed a 44% improvement in function, compared with 32% improvement for patients receiving placebo ($p<0.001$).^{22,27} (Figure 3)

According to a long-term, randomised, double-blind, relapse prevention study, adult MDD patients receiving desvenlafaxine 50 mg per day experienced significantly longer time to relapse over 6 months compared with those receiving placebo. The data showed that the probability of relapse with desvenlafaxine 50 mg per day was 14.3% versus 30.2% with placebo 6 months later. Desvenlafaxine 50 mg per day was generally well tolerated over 6 months of treatment.²⁸

Practical tips for prescribing desvenlafaxine

Pooled analysis of data from nine double-blind, randomised, placebo-controlled,

Figure 3. Improvement in mean SDS total score from baseline^{22,26}



fixed- or flexible-dose, 8-week trials of desvenlafaxine 50, 100, 200 and 400 mg per day in adults aged 18 years or older with MDD, demonstrated that the optimal dose of desvenlafaxine was 50 mg per day, with no additional benefit for greater doses as measured by HAM-D17 total score. Discontinuation rates due to adverse events were greater at doses above 50 mg per day.^{24,25}

The starting dose is also the recommended therapeutic dose: desvenlafaxine 50 mg once daily, with or without food. Dose escalation above 100 mg per day is not recommended. In patients with hepatic impairment, a dose of 50 mg per day is recommended. While no dosage adjustment is required solely on the basis of age, it is prudent for clinicians to consider the possibility of reduced renal clearance associated with advanced age when determining dosage. Patients with severe renal impairment or end-stage renal disease (ESRD) should be administered desvenlafaxine at 50 mg every other day. Also, desvenlafaxine dose should not be escalated in patients with moderate or severe renal impairment or ESRD. When discontinuing therapy, a gradual dose reduction is recommended over abrupt cessation whenever possible.¹³

Conclusion

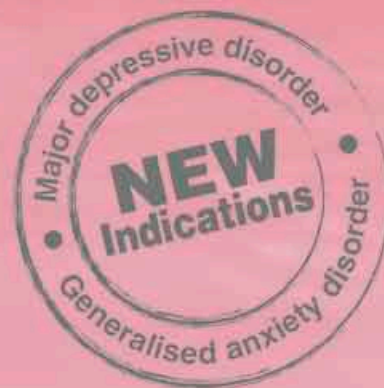
Desvenlafaxine is a new first-line pharmacological option for MDD with good efficacy in terms of clinical and func-

tional improvements. It has a good tolerability profile with minimal drug-drug interactions. The starting dose is also the recommended therapeutic dose: desvenlafaxine 50 mg once daily, with or without food. Dose escalation above 100 mg per day is not recommended. Commonly observed adverse reactions in patients taking desvenlafaxine 50 mg include nausea, dizziness, hyperhidrosis, constipation and decreased appetite. Nausea is generally mild to moderate with prevalence decreasing to placebo-like levels within 1 week. It is different from venlafaxine, and other antidepressants. Other medications, including venlafaxine, can be switched to desvenlafaxine if not effective or tolerable.

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Atypical power in major depressive disorder and generalised anxiety disorder



- Symptom relief* as early as Week 1 in MDD and Day 4 in GAD¹⁻³
- Broad-spectrum improvement including insomnia¹⁻⁵
- Prevention of recurrence with good tolerability⁴⁻⁶

*measured by MADRS total score for MDD and HAM-A total score for GAD

AstraZeneca

Further information is available on request.
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quetiapine

Abbreviated Prescribing Information:

Presentation: Quetiapine fumarate extended-release tablet. **Indications:** **Bipolar Disorder:** Maintenance treatment of bipolar I disorders, as monotherapy or in combination with lithium or sodium valproate, for the prevention of relapse/recurrence of manic, depressive or mixed episodes. Treatment of depressive episodes associated with bipolar disorder. Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate. **Schizophrenia:** Treatment of schizophrenia, prevention of relapse and maintenance of clinical improvement during continuation therapy. **Major Depressive Disorder:** Treatment of recurrent major depressive disorder (MDD) in patients who are intolerant of, or who have an inadequate response to, alternative therapies. **Generalised Anxiety Disorder:** Treatment of generalised anxiety disorder (GAD). **Dosage:** **Schizophrenia:** Once-daily in the evening. Initial dose: 300 mg (Day 1), 600 mg (Day 2) and up to 800 mg after Day 2. Range: 400-800 mg/day depending on clinical response & tolerability of patient. Same dosage is used for maintenance therapy. **Bipolar Disorder:** Acute Mania: Starting daily dose is: 300 mg (Day 1) & 600 mg (Day 2) & up to 800 mg (after Day 2), alone or in combination with a mood stabilizer. Range: 400-800 mg/day. **Bipolar Depression:** Starting dose is 50mg (Day 1) & 100 mg (Day 2) & 300 mg (Day 3) & 300 mg (Day 4). Titration can be up to 400 mg on Day 5 and up to 600 mg by Day 8. **Maintenance treatment:** Use same dose as active treatment for prevention of manic, depressive or mixed episodes in bipolar disorder. Range: 300-800 mg/day. **Recurrent major depressive disorder:** Once-daily in the evening. Initial dose: 30 mg (Day 1 & 2), increased to 150 mg on Day 3 & 4. Usual effective dosage: 150 mg. Range of 50 - 300 mg/day. Same dosage is used for maintenance. **Generalised Anxiety Disorder:** Initial dose: 50 mg (Day 1 & 2), increased to 150 mg on Day 3 & 4. Range of 50 - 150 mg/day. **Switching from Seroquel IR:** Switch at equivalent total daily dose. Individual adjustments may be necessary. **Elderly or hepatic impairment patients:** Slower dose titration is recommended. Initial dose: 50 mg/day up to target dose depending on clinical response and tolerability of patient. In elderly MDD, initial dose: 50 mg (Day 1-3), increased to 150 mg (Day 4), 150 mg (Day 8) and then up to 300 mg. In elderly GAD, initial dose: 30 mg (Day 1-3), increased to 100 mg (Day 4), up to 150 mg on Day 8. **Renal impaired patients:** No dosage adjustment needed. **Contraindications:** Hypersensitive to the active substance or excipients of this product. **Precautions:** Not recommended for below 18y old; clinical worsening and suicide risk associated with psychiatric disorders; somnolence; severe neutropenia; known cardiovascular & cerebrovascular disease; Conditions predisposing to hypotension; orthostatic hypotension; extrapyramidal symptoms; history of seizures; tardive dyskinesia; neuroleptic malignant syndrome; not approved in elderly patients with dementia-related psychosis; established diabetes mellitus; dysphagia; jaundice development; venous thromboembolism; galactose intolerance; pregnancy & lactation. **Interactions:** CYP3A4 inhibitors; centrally acting drugs; grapefruit juice; thioridazine; lorazepam; levodopa and dopamine agonists; carbamazepine; phenytoin; ketoconazole; ADHD medications & cardiovascular medicines that cause electrolyte imbalance or to increase QTc interval. **Undesirable effects:** tachycardia; vision blurred; mild asthenia; peripheral edema; irritability; increased appetite; dysarthria; elevations in serum transaminases (ALT, AST); syncope; rinitis; abnormal dreams & nightmares and elevations in serum prolactin. **Full local prescribing information is available upon request. APL-HK-SXR-0810**

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MDD: Major Depressive Disorder; GAD: Generalised Anxiety Disorder; MADRS: Montgomery Åsberg Depression Rating Scale; HAM-A: Hamilton Rating Scale - Anxiety

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Management of Moderate-to-Severe Alzheimer's Disease: New Evidence to Supplement Guidelines



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Key words:

dementia (認知障礙症或癡呆症),
moderate (中度), severe (嚴重),
pharmacotherapy (藥物治療)

Most trial evidence in the drug treatment of Alzheimer's disease (AD) is derived from patients in the mild-to-moderate stage, but much less is known about the effectiveness of drugs in moderate-to-severe AD; fewer than 10 studies have focused on the effectiveness of anti-dementia drugs, namely, acetylcholinesterase inhibitors and the NMDA-receptor antagonist, memantine, in more severe AD.

or not to stop or continue anti-dementia pharmacotherapy once patients reach the moderate-to-severe stage. Some, for example the American College of Physicians (ACP) guideline,¹ remain vague about whether drugs might be useful in more severe AD, while others, such as the United Kingdom (UK) National Institute for Health and Clinical Excellence (NICE) guidance, explicitly recommend that only memantine should be used for moderate-to-severe disease.² Others, however, suggest that either acetylcholinesterase inhibitors or memantine, or both, can be used in this stage.³ In view of these differences and the costs of these anti-dementia drugs, trial evidence to guide daily practice is urgently needed.

Guidelines

Guidelines from different organisations (Table) vary on the question of whether

Table. Guidelines on pharmacotherapy in moderate-to-severe AD		
Guideline	Specific recommendations according to disease stage	Recommendations
American College of Physicians ¹	No	<ul style="list-style-type: none"> • Recommendation 1: Base decision to initiate a trial of therapy with an acetylcholinesterase inhibitor or memantine on individualised assessment. • Recommendation 3: Clinicians to base choice of pharmacological agents on tolerability, adverse effect profile, ease of use, and cost of medications.
United Kingdom National Institute for Health and Clinical Excellence ²	Yes	<ul style="list-style-type: none"> • Memantine recommended for: moderate AD when intolerant or contraindicated to acetylcholinesterase inhibitors; severe AD. • Treatment to be continued in these stages only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms, with input from caregivers.
Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia ³	Yes	<ul style="list-style-type: none"> • Non-pharmacological approaches recommended for mood and agitation problems. • Antipsychotic therapy may be necessary occasionally. • Patients should be closely monitored at least 3–4 monthly if on drug treatment. • Therapy with an acetylcholinesterase inhibitor, or memantine, or both, may be useful for selected patients, until clinical benefits can no longer be demonstrated. • Therapeutic aims include patient and caregiver quality of life, maintaining functions and optimising comfort.

Evidence

A multicentre, double-blind, randomised controlled trial, which was co-funded by the UK Medical Research Council and the UK Alzheimer's Society and published in the March 2012 issue of the *New England Journal of Medicine*,⁴ might help physicians making this clinical decision. Investigators in the DOMINO study (Donepezil and Memantine in Moderate to Severe Alzheimer's Disease) randomised 295 community-living moderate-to-severe AD patients on stable doses of the acetylcholinesterase inhibitor, donepezil, into four treatment arms: continue donepezil; discontinue donepezil; substitute donepezil with memantine; or add memantine to donepezil. Patients received the medications for 1 year. Primary outcomes were cognition as reflected by the Mini-Mental State Examination (MMSE) score and activities of daily living (ADL) (Bristol ADL Scale).⁴

“Cognitive benefit associated with continued treatment into moderate-to-severe AD, was 32% with donepezil”

Patients had baseline MMSE scores of 5 to 13 out of 30, and after 1 year, those who had stopped all active drug treatment deteriorated significantly faster than those in the other three groups. In terms of MMSE or ADL scores, combined donepezil and memantine was no more effective than either donepezil or memantine alone. The 1.9 point difference in MMSE scores between those who continued treatment with donepezil and those who stopped, was larger than the pre-defined clinically significant difference of 1.4 points. However, the mean difference in ADL score between these two groups was

-3.0 points, which was smaller than the pre-defined clinically significant difference of -3.5 points. Compared to no active drug treatment, the cognitive benefit associated with continued treatment into moderate-to-severe AD, was 32% with donepezil, and 20% among patients switched to memantine. The functional benefit compared to no treatment was 23% with continued donepezil, and 11% with a switch to memantine.

Evidence Supplementing Guidelines

The DOMINO findings support the Canadian guidance,³ that some drug treatment is better than no treatment in moderate-to-severe AD, and adds to the ACP¹ and NICE² recommendations that both cholinesterase inhibitors and memantine may benefit such patients. Greater benefit of donepezil in DOMINO appears to contradict NICE guidance on the choice of drug for moderate-to-severe AD. These results are less likely to be biased in favour of either drug manufacturer than industry-sponsored studies, because DOMINO was funded by independent agencies. It is noteworthy that the cognitive benefits appeared larger for those with moderate AD (MMSE 10–13) than those with severe AD (MMSE 5–9).⁴ However, MMSE may not be a very accurate gauge of AD severity, especially in its later stages. Furthermore, DOMINO did not measure other domains that are important to patients and caregivers, such as language, praxia and functional independence.

Other Important Issues in Moderate-to-Severe Dementia

Other interesting data that the authors did not highlight were the compliance rate and mortality among this cohort of patients with more advanced AD. The annual mortality rate of the 295 participants was 13.2%.⁴ The compliance rate was below 70% in 26% to 42% of those on either one or two active drugs,

but was as high as 60% among patients with no active drugs.⁴ Factors affecting drug compliance might include sick days, hospitalisations, or simply caregivers feeling treatment to be futile, as the highest non-compliance rate was among those receiving no active treatment.

Clinicians treating dementia patients should be aware that patients with moderate-to-severe AD will start to become vulnerable to its medical complications, in addition to other co-morbidities common in old age. For example, impairment of vital functions, such as dysphagia, weakened immunity, poor nutrition, high risk for falls and fractures, will start to take their toll. Caregivers will be burdened with the patient's personal care, hospitalisations and medical consultations, end-of-life care decisions, as well as medication management. Given the frailty of the patient and the high caregiver burden in the end stage of life, all prescriptions should be individualised after thorough discussion with the family. Some may opt for further maintenance of the remaining cognition or function, while others may prefer minimal medical intervention with comfort care. The hopes and expectations of each patient and family will differ. When the patient becomes bedridden, doubly incontinent, aphasic, and there are no meaningful functions or cognition to preserve, good nursing care and advance care planning may be more beneficial than medications.

Conclusion

Recent evidence suggests that patients with moderate-to-severe AD on stable doses of donepezil may continue to show cognitive and functional benefits with donepezil or memantine. However, combining these drugs confers no additional benefit.

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diminish the effectiveness of ropinirole. There is no pharmacokinetic interaction between ropinirole and L-dopa or domperidone which would necessitate dosage adjustment of these drugs. No interaction has been seen between ropinirole and other drugs commonly used to treat Parkinson's disease. Ropinirole is principally metabolised by the cytochrome P450 enzyme CYP1A2. Hence, in patients already receiving REQUIP PD, the dose of REQUIP PD may need to be adjusted when drugs known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn. Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), REQUIP PD treatment may be initiated in the normal manner. However, if HRT is stopped or introduced during treatment with ropinirole, dosage adjustment may be required. No information is available on the potential for interaction between ropinirole and alcohol. Smoking is known to induce CYP1A2 metabolism, therefore if patients stop or start smoking during treatment with REQUIP PD, adjustment of dose may be required. **Pregnancy and Lactation:** It is recommended that REQUIP PD is not used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus. REQUIP PD should not be used in nursing mothers as it may inhibit lactation. **Effects on Ability to Drive and Use Machines:** Patients should be cautioned about their ability to drive or operate machinery whilst taking REQUIP PD because of the possibility of somnolence and of dizziness (including vertigo). Patients should be informed about very rare cases of sudden onset of sleep without any prior warning or apparent daytime somnolence and should be cautioned that their safety and that of others is at risk should this happen when driving or operating machinery. If patients develop significant daytime sleepiness or episodes of falling asleep during activities that require active participation, patients should be told not to drive and to avoid other potentially dangerous activities. **Adverse Reactions: Clinical Trial Data** Adverse Drug Reactions Reported from Patients with Parkinson's Disease: Hallucinations, confusion, somnolence, syncope, dyskinesia (In patients with advanced Parkinson's disease, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia), dizziness (including vertigo), Postural hypotension¹, hypotension, nausea, abdominal pain, vomiting, dyspepsia, constipation, Oedema peripheral (including leg oedema) **Adverse Drug Reactions Reported During Clinical Trials in Patients with Restless Legs Syndrome:** nervousness, dizziness (including vertigo), somnolence, syncope, nausea, vomiting, abdominal pain, fatigue **Post Marketing Data** Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus), psychotic reactions (other than hallucinations) including delusion, paranoia, delirium, impulse control symptoms, increased libido including hypersexuality, pathological gambling, extreme somnolence, sudden onset of sleep, hypotension, postural hypotension **Overdose:** The symptoms of ropinirole overdose are generally related to its dopaminergic activity. These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide. Version number: GD519/PI/10 API REQUIP, REQUIP PD and the REQUIP PD logo are trademarks of the GlaxoSmithKline group of companies.

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Initial Treatment of Early Parkinson's Disease



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Key words:

Parkinson's disease (帕金森症),
dopamine (多巴胺)

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease with the hallmark physical signs of tremor, rigidity and bradykinesia. Patients with advanced disease have complex motor and non-motor problems and are usually managed by neurologists. On the other hand, patients with early-stage PD most often present their symptoms to primary care physicians. Although the choice of the first anti-PD agent in early-stage patients can rapidly effect profound motor improvements, it can also result in subsequent motor complications. This article highlights the current approach to the initial management of newly diagnosed PD.¹

When to start treatment?

Treatment should be initiated once the signs and symptoms begin to interfere with the patient's daily-living activities.

Traditional levodopa treatment

Levodopa remains the gold standard for alleviating PD symptoms, with its advantage being rapid onset of action, and is particularly effective for akinetic symptoms. However, its use is associated with common early side effects, which include orthostatic hypotension, somnolence and nausea.

Limitations of Levodopa

From clinical observations, patients receiving chronic levodopa therapy tend to develop motor complications, which occur in 50% to 90% of PD patients who

have received levodopa for 5 to 10 years.² They include 'on-off' phenomenon, 'freezing', 'wearing off' (end-of-dose failure) and dyskinesias (involuntary movements associated with loose muscle tone). Patients with 'on-off' phenomenon experience abrupt changes in muscle tone, repeatedly switching from rigidity ('off') to a normal or dyskinetic state ('on') and then back to rigidity ('off') within minutes.

Motor complications

How frequent is levodopa-induced dyskinesia?

The known risk factors for developing motor complications are disease severity, duration of therapy, young age, and levodopa dosage. The risk of developing motor complication within 5 years of starting levodopa therapy is at least 50%.² They are a particular problem in patients with young-onset PD (20–40 years), of whom 100% develop dyskinesia by 6 years.³ The incidence of dyskinesia declines with age. In patients with PD onset at 70 years or later, the 5-year incidence rate was 16%; however, for patients with PD onset at 40–59 years, the incidence was significantly higher, at 50%.⁴

Another concern regarding the initiation of PD treatment with levodopa is its 'priming' effect. In primates with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure, even a single levodopa dose primes for the development of dyskinesia.⁵ Dopamine agonists do not induce dyskinesia when administered to previously untreated parkinsonian animals, but induce dyskinesia in animals with previous exposure to levodopa.⁶ While the relevance of prior levodopa treatment in human PD patients remains unclear, these findings raise concerns that early treatment with levodopa may prime for the development of dyskinesia.

Dopamine sparing strategy

Since younger patients are more likely to develop levodopa-induced motor complications, it is reasonable to initiate dopamine agonists as initial PD therapy, in an attempt to delay the onset of motor complications.² Posthoc analysis of a study⁷ investigating the relationship between the choice of initial PD treatment (levodopa vs. ropinirole) and the time-to-onset of dyskinesia, demonstrated that add-on levodopa to initial monotherapy with dopamine agonists substantially increases the risk of dyskinesia, with the rate of dyskinesia development similar to that of levodopa as initial monotherapy. However, the onset of dyskinesia was found to be delayed by 3 years. Thus, dopamine-sparing strategy delays the occurrence of dyskinesias until the time when levodopa therapy is started, and extends the duration of the early treatment 'honeymoon' period for dyskinesias.

Dopamine agonists

Although dopamine agonists are less effective than levodopa, they remain the first-line choice in the dopamine-sparing strategy. The advantages of using dopamine agonists are the reduced risk of inducing dyskinesia and motor fluctuations.⁸⁻¹⁰ Common adverse effects associated with dopamine agonist use are ankle oedema, drowsiness, orthostatic hypotension, nausea and hallucinations.

Bromocriptine is an ergot-derived dopamine agonist. It has low potency and the potential for causing valvular heart disease. Hence, non-ergot agents should be considered; ropinirole, pramipexole, and rotigotine are the available options.

Ropinirole and pramipexole are to be taken orally three times a day. An extended-release formulation of ropinirole is available, allowing a once-daily dosing for better patient convenience and enhanced patient adherence. Rotigotine patches are also available for transdermal administration, and offer a viable alternative when a non-oral route of administration is desired.

Other dopamine-sparing agents

Amantadine

Amantadine is a mild indirect dopaminergic agent. Its adverse effect profile

(peripheral oedema, rash, confusion, and hallucination) limits its suitability for elderly patients or those with cognitive impairment. Amantadine is more effective when used in combination with other anti-PD agents, but is associated with a rapid loss of therapeutic response when administered as monotherapy.¹¹

Anticholinergic agents

Anticholinergic agents, such as trihexyphenidyl, are useful in the symptomatic treatment of PD tremor, but may not cover other motor symptoms such as rigidity and bradykinesia. Adverse effects associated with anticholinergic agents include blurred vision, urinary retention, constipation, and dry mouth. They can also increase the severity of cognitive impairment, making them undesirable for use in elderly patients.

MAO-B inhibitors

Selegiline is a selective monoamine oxidase type B (MAO-B) inhibitor. While it provides a weak anti-PD effect, it has yet been established as a neuroprotective agent.

Rasagiline is a novel selective MAO-B inhibitor. It is suitable for patients with early symptoms of PD and does not require titration. Rasagiline is FDA-approved for the treatment of early PD, and has been shown to be effective as monotherapy and as an adjunct to dopaminergic therapy.^{12,13} While human trials have yielded inconsistent findings, its neuroprotective effects have been demonstrated in animal models. However, the potential of rasagiline in altering the long-term course of PD remains controversial.

Which drug first?

As older patients (>70 years) are less likely to develop dyskinesia, levodopa remains a reasonable choice for initial therapy, as it offers effective symptomatic control. However, in younger patients who are more likely to develop levodopa-induced motor complications, it is reasonable to adopt a dopamine-sparing strategy, by using dopamine agonists as the drug of choice for first-line treatment. Other agents, such as amantadine, anticholinergic agents and MAO-B inhibitors, provide weak symptomatic relief in early PD. They help delay the introduction of

levodopa, in turn delaying the onset of motor complications.

Conclusion

Levodopa is the most commonly prescribed medication for PD. However, its usage is limited by the development of dyskinesia and dystonia after prolonged administration. While it is less of a concern in older patients (>70 years), about half of younger patients (40–59 years) develop dyskinesia within 5 years of starting levodopa therapy. In fact, there are concerns that the initiation of levodopa therapy may even prime the onset of dyskinesia. To delay the onset of motor complications, the adoption of a dopamine-sparing strategy is therefore a reasonable choice in younger patients (<60 years). Rasagiline, a novel MAO-B inhibitor, is an option for initial monotherapy in early PD patients with mild symptoms. Dopamine agonists provide effective motor symptom relief with good tolerance profiles; they can also delay the onset of motor complications and the introduction of levodopa.

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¹ IMS Health December 2010

² HKAPI data December 2010

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Management of Chronic Hepatitis B with Entecavir



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Introduction

Manifestations of chronic hepatitis B virus (HBV) infection range from carrier state to chronic hepatitis, compensated or decompensated cirrhosis and hepatocellular carcinoma (HCC). This article reviews the natural history of chronic HBV (CHB) infection and its management with entecavir.

Predictive factors of chronic HBV infection

Life-time risk of a liver-related death among Chinese CHB patients has been estimated at 40% for males and 15% for females.¹ Estimated 5-year rates of progression are 12–20% from CHB to cirrhosis, 20–23% from compensated cirrhosis to hepatic decompensation and 6–15% from compensated cirrhosis to HCC.² The 5-year survival is 85% for compensated cirrhosis and 14–35% for decompensated cirrhosis.

Serum HBV DNA level is an independent risk factor for HCC. In a community-based study in Taiwan (REVEAL-HBV) with a median follow-up of 11 years, higher incidence of HCC was associated with the HBV DNA level at study entry;³ HBV DNA levels $\geq 2,000$ international units (IU)/mL were associated with significantly higher risk of HCC.

Prolonged low-level viraemia causing continual liver damage, as reflected by alanine aminotransferase (ALT) levels of $>0.5X$ upper limit of normal (ULN), is the most likely reason for developing complications. Patients with ALT levels of $0.5-1X$ ULN and $1-2X$ ULN had significantly increased risk for developing complications compared with patients with ALT levels $<0.5X$ ULN ($p < 0.0001$ for both).⁴

Goal of treatment

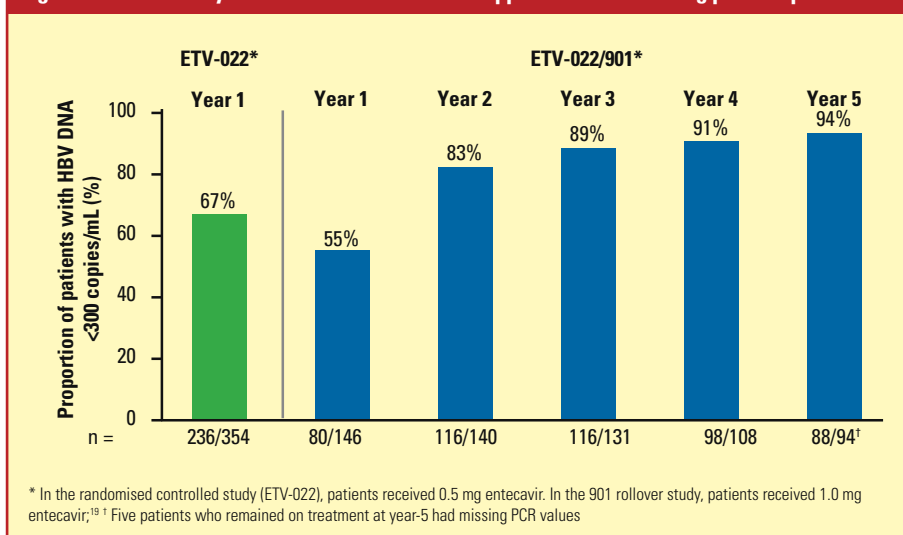
The ultimate goal of antiviral therapy in CHB is to eradicate HBV from the patient. However, this is impossible, due to the persistence of stable, long-enduring, covalently-closed circular DNA (cccDNA) in the nucleus of infected hepatocytes.⁵ The cccDNA acts as a template that piggybacks the host's transcriptional processes to produce the viral RNAs required for viral replication.⁶ The HBV genome integrates into the host genome and induces oncogenesis.⁷

At present, the achievable goal of therapy is preventing complications. The efficacy of the oral nucleoside/nucleotide analogues has been established in randomised controlled trials. These include normalisation of ALT, HBV DNA suppression, and the reversal of histological activity. For example, lamivudine has been shown to slow disease progression and decrease the incidence of HCC in patients with advanced fibrosis, relative to placebo.⁸ The major disadvantage was the development of genotypic resistance in 76% of patients after 8 years of treatment.⁹

Indication for treatment

Treatment guidelines vary among countries. In America, there are two guidelines. Firstly, a panel of US hepatologists recommend treatment when the HBV DNA level is $>20,000$ IU/mL in HBV e-antigen (HBeAg)-positive patients and 2,000 in HBeAg-negative patients with an elevated ALT level (>30 IU/L for men and >19 IU/L for women).¹⁰ All patients with decompensated cirrhosis, regardless of their serum HBV DNA level, should be treated. Secondly, the American Association for the Study of Liver Diseases treatment guidelines are similar, but define elevated ALT as $2X$ ULN.¹¹ In

Figure 1. Entecavir 5-year clinical trial HBV DNA suppression data: HBeAg positive patients¹⁹



contrast, the European Association for the Study of the Liver guidelines, recommend treatment for those with HBV DNA $\geq 2,000$ IU/mL and elevated ALT, for both HBeAg-positive and negative CHB.¹² Lamivudine, adefovir and telbivudine are not recommended because of a high rate of resistance mutation. Entecavir and tenofovir are potent HBV inhibitors with a high barrier to resistance; accordingly, they are confidently used as first-line monotherapies.

Entecavir

Entecavir is an orally-administered cyclopentyl guanosine analogue for treating CHB infection in adults with evidence of active viral replication and either persistent elevation in serum aminotransferases or histologically active disease. Entecavir is phosphorylated intracellularly to active guanosine triphosphate, which competes with the natural substrate deoxyguanosine triphosphate and effectively inhibits HBV DNA polymerase. Entecavir inhibits HBV DNA polymerase priming, reverse transcription of pre-genomic messenger RNA, and synthesis of positive-stranded HBV DNA and incorporation prior to chain termination.^{13,14} These mechanisms reduce HBV DNA synthesis.

Entecavir reduces HBV DNA replication 2,200 times better than lamivudine.¹⁵ In an early phase II trial comparing entecavir with lamivudine,

higher rates of virological suppression were observed in the entecavir group (HBV DNA negativity rate: 83.7% for entecavir, 57.5% for lamivudine, $p=0.008$).¹⁶ The subsequent phase III trial of 715 treatment-naïve HBeAg-positive patients showed significantly higher rates of histological, virological and biochemical improvement in those treated with entecavir compared with lamivudine.¹⁷ More patients in the entecavir group than in the lamivudine group had undetectable serum HBV DNA (67% vs. 36%, $p<0.001$). The mean reduction in serum HBV DNA from baseline to week 48 was greater with entecavir than with lamivudine (6.9 vs. 5.4 \log_{10} copies/mL, $p<0.001$). Similar results were obtained in a phase III study with 648 treatment-naïve HBeAg-negative CHB patients (undetectable serum HBV DNA: entecavir group 90%, lamivudine group 72%, $p<0.001$).¹⁸ The mean reduction in serum HBV DNA levels from baseline to week 48, was greater with entecavir than with lamivudine (5.0 vs. 4.5 \log_{10} copies/mL, $p<0.001$).

HBeAg-positive chronic hepatitis

Entecavir treatment achieves HBeAg seroconversion in about 20% of HBeAg-positive patients.¹⁷ There is a 5–7 \log_{10} reduction in mean HBV DNA levels. The rate of virological resistance is around 1% with up to 5 years of follow-up.

A multicentre trial randomised 715 HBeAg-positive patients to receive entecavir or lamivudine for 48 weeks. More

patients in the entecavir than the lamivudine group had histologic improvement after 48 weeks (72% vs. 62%, $p=0.009$). More patients in the entecavir group than in the lamivudine group had normalisation of ALT levels (68% vs. 60%, $p=0.02$). No viral resistance to entecavir was detected.¹⁷ A follow-up study described a subset of 146 patients who received continuous entecavir therapy for up to 5 years;¹⁹ 94% achieved HBV DNA negativity (<300 copies/mL) by the fifth year (Figure 1).

HBeAg-negative chronic hepatitis

A multicenter trial randomised 648 HBeAg negative patients to entecavir or lamivudine for up to 96 weeks. Histologic improvement, defined as a ≥ 2 point reduction in the Knodell necro-inflammatory score at 48 weeks, was significantly more common in the entecavir group (70% vs. 61%, $p=0.01$). ALT was normalised significantly more often in the entecavir group (90% vs. 72%).¹⁸

Decompensated cirrhosis

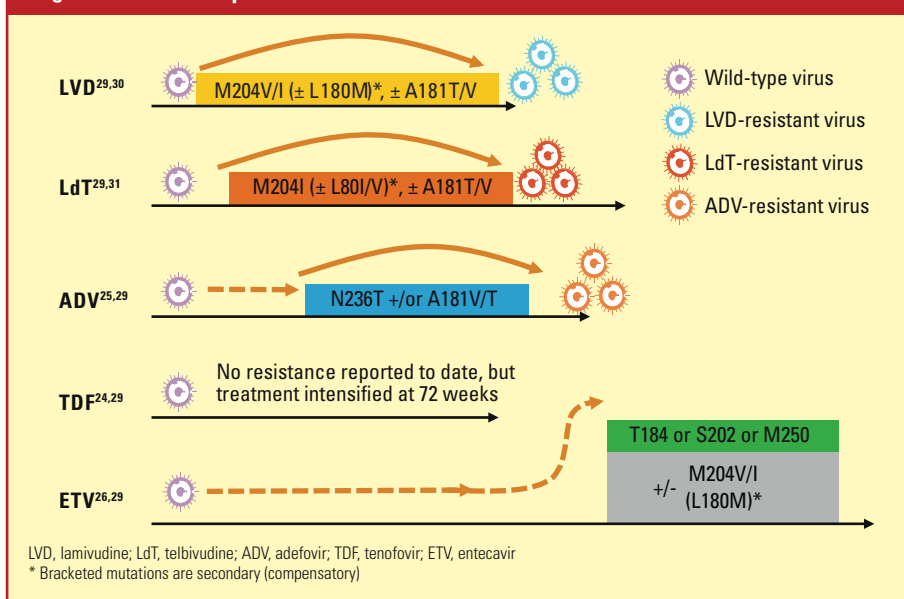
Entecavir treatment is efficacious in arresting HBV replication in compensated or decompensated liver disease. In addition, entecavir markedly improved the underlying hepatic reserve in decompensated cirrhotic patients, mostly within 6 months of treatment.

There are two studies on the efficacy of entecavir in decompensated liver disease. Firstly, in treatment-naïve patients who received entecavir (0.5 mg daily) for one year, 49% had improvement in Child-Turcotte-Pugh score of ≥ 2 points. HBV DNA negativity was achieved in 92% patients.²⁰ A second study randomised 191 patients with decompensated HBV to entecavir (1 mg daily) or adefovir (10 mg daily) for up to 96 weeks. HBV DNA negativity (<300 copies/mL) was achieved in 57% and 20%, respectively, of patients with entecavir and adefovir. Cumulative death rates were 23% for entecavir and 33% for adefovir.²¹

Resistance to entecavir

Entecavir has a high barrier to resistance, requiring three mutations before resistance develops. Resistance to entecavir develops through a two-hit

Figure 2. Resistance profile: The extent of genetic barrier to resistance can impact long-term treatment options



mechanism.²² Initially, mutants that are resistant to lamivudine (rtM204V/I and rtL180M) are selected because they are less sensitive to entecavir. In addition, mutations at rtI169, rtT184, rtS202, and/or rtM250 are selected. No resistance was observed after 48 weeks of treatment in the two large multinational trials of nucleoside-naïve patients.^{17,18} Entecavir resistance occurred at a rate of only 1.2% after 5 years of therapy.¹⁹

In contrast, the presence of lamivudine resistance mutations increases the risk of developing entecavir resistance. The 5-year cumulative probability of genotypic resistance and virologic breakthrough were 51% and 43%, respectively.²³

Safety

Entecavir has an excellent safety profile. On-treatment flares with ALT >10X ULN were observed in only 2% of nucleoside-naïve patients during 48 weeks of treatment. Regular frequent monitoring of renal function is not required, as it is with nucleotide analogues such as tenofovir and adefovir.²⁴⁻²⁶

Lactic acidosis has been reported in five patients with advanced decompensated cirrhosis in a case report (model for end-stage liver disease score ≥ 20).²⁷ However, severe lactic acidosis was not observed in several ongoing trials of entecavir in patients with decompensated cirrhosis.

Treatment endpoint

Many guidelines suggest that treatment endpoints include HBeAg seroconversion for HBeAg-positive patients, undetectable serum HBV DNA, and normalisation of ALT. Although these guidelines may apply to patients who acquire the HBV infection during adolescence or adulthood, they are not suitable for most Asian HBV carriers infected in early life.²⁸ Cirrhosis complications and HCC often occur in Asians despite HBeAg seroconversion, HBV DNA levels less than 10^4 copies/mL, or ALT levels between 0.5 and 2X ULN. The ideal treatment endpoints are permanent suppression of HBV DNA to levels undetectable by polymerase chain reaction and reduction of ALT levels to less than 0.5X ULN.

Long-term treatment is required in most patients. Almost all patients have virological relapse after stopping nucleos(t)ide analogue (Figure 2).^{24-26,29-31} Severe ALT flares (>10X ULN) were observed in 6% of patients after discontinuation of entecavir treatment.

Long-term therapy can reverse liver fibrosis and cirrhosis.³² In patients with advanced fibrosis or cirrhosis, improvements in liver histology and Ishak fibrosis scores were observed after entecavir therapy for 6 years. The mean change from baseline in Ishak fibrosis and Knodell necroinflammatory scores were -2.2 and -7.6, respectively. Therefore,

in patients with liver cirrhosis, entecavir should be continued to attain long-term HBV DNA suppression.

Conclusion

Treatment:

- Patients with CHB should be treated when they reach the threshold for treatment, as indicated by the various guidelines.
- Early treatment should be initiated in 35–40 year-old patients with advanced histology or clinical evidence of cirrhosis.
- Treatment for both HBeAg-positive and HBeAg-negative patients should be on a long-term basis, possibly until HBV surface antigen seroconversion.³³
- Permanent suppression of HBV replication, with reversal of fibrosis and cirrhosis, is achievable.

Entecavir:

- Entecavir is effective in suppressing HBV DNA, ALT normalisation, and histologic improvement in nucleoside-naïve patients with CHB infection.
- Long-term treatment can reverse fibrosis in patients with liver cirrhosis.
- Entecavir has a high mutation barrier. Resistance to entecavir is rare (approximately 1% after 5 years treatment) in nucleoside-naïve patients.
- Entecavir is safe and no routine monitoring of renal function is required.

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