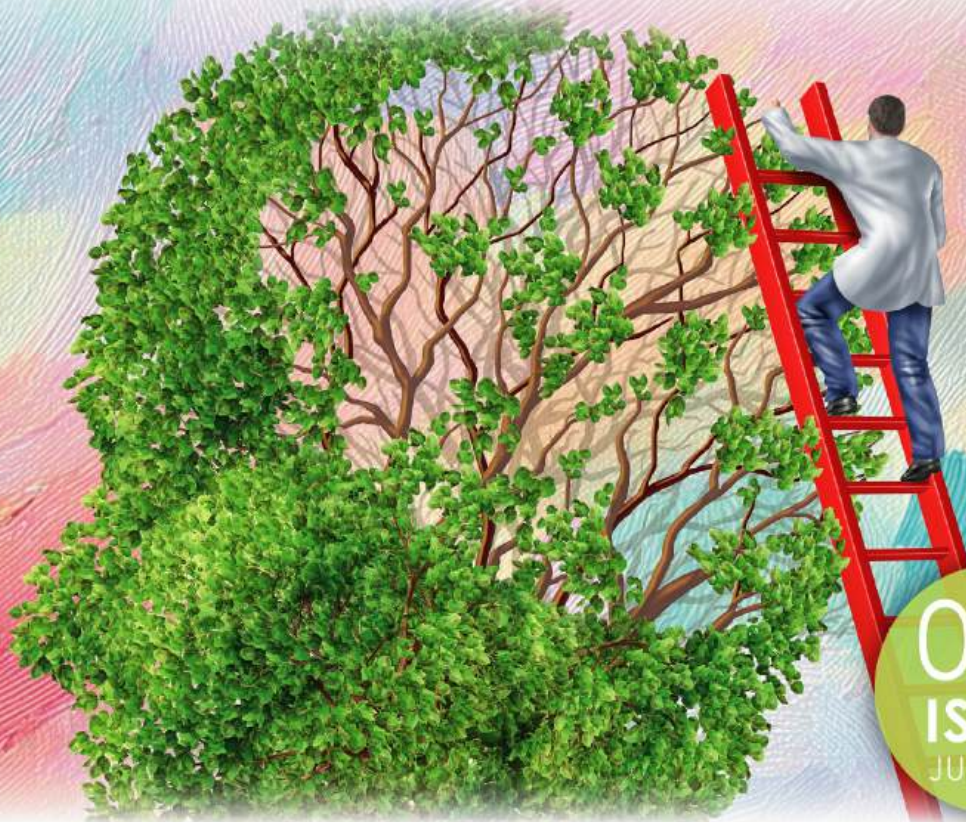




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## Hope in Motion: Clinical Progress and Social Support for Parkinson's



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ISSUE  
JUN 2026

**FOCUS:** ASCO 2026: Unprecedented Seven-Year Results from CROWN Redefine ALK-Positive NSCLC Treatment

Advancing Schizophrenia Care with INTEGRATE: Practical, Global, Algorithm-based Guidance

Advances in the Management of Marginal Zone Lymphoma with Zanubrutinib

Coffee or Tea? Caffeine Consumption—a New Perspective of Dementia Prevention



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Dear Reader,

Welcome to the June 2026 issue of V.Pulse!

In this issue, our Feature Story examines the evolving landscape of Parkinson's disease (PD), an incurable condition that significantly impacts the aging population. It highlights promising advances in management, including  $\alpha$ -synuclein-targeted therapies, stem cell approaches, drug repurposing, deep brain stimulation, and non-pharmacological strategies—offering renewed hope while underscoring the need for continued research.

In our Focus Section, we spotlight key insights from ASCO 2026 on ALK-positive non-small cell lung cancer. Updated seven-year results from the CROWN study reinforce lorlatinib's role as a highly effective first-line therapy, with durable systemic and intracranial control, reflecting the transformative impact of targeted treatments.

Our Epoch Section explores a timely question—*Coffee or Tea?*—through the lens of emerging evidence on caffeine consumption and dementia prevention.

As always, our mission is to deliver concise, clinically relevant insights that connect innovation with practice.

We hope you enjoy this issue.

Warm regards,

**Dr. Feng Xue**  
MPH, PhD  
Managing Editor, V.Pulse

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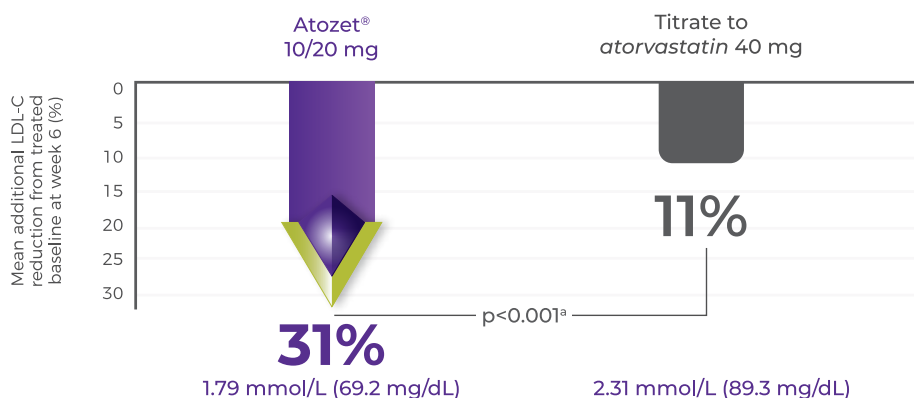
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# Strike Strong with Confidence on LDL-C

The image is for illustration purposes only.

In a clinical study of moderately high-risk patients with hypercholesterolemia on atorvastatin 20 mg who were randomized to receive either Atozet® 10/20 mg or atorvastatin 40 mg<sup>1</sup>

From atorvastatin 20 mg



► Mean treated baseline LDL-C for patients receiving Atozet® 10/20 mg (n=92) was 3.10 mmol/L (119.9 mg/dL) and 3.05 mmol/L (117.9 mg/dL) for those titrated to atorvastatin 40 mg (n=92).

► Target: Patients with hypercholesterolemia at moderately high risk of CHD to achieve LDL-C <2.6 mmol/L (100 mg/dL).

**Atozet® 10/20 mg provided superior LDL-C lowering efficacy versus doubling the dose of atorvastatin 20 mg**

**Prescribe Atozet® for moderately high-risk hypercholesterolemia patients with coronary heart disease who require LDL-C reduction beyond what statin alone can achieve.**

LDL-C = Low-density lipoprotein cholesterol

Study design: The TEMPO study was an international, multicenter, double-blind, randomized, parallel-group, titration 6-week study, including 196 patients. The study was designed to evaluate the efficacy and safety profile of Atozet® 10/20 mg compared with doubling atorvastatin to 40 mg/day in patients with hypercholesterolemia at moderate risk of CHD who did not reach LDL-C goal <2.6 mmol/L (<100.5 mg/dL) with atorvastatin 20 mg. Patients receiving atorvastatin 20 mg with LDL-C 2.6 mmol/L (100.5 mg/dL) and 4.13 mmol/L (159.7 mg/dL) were randomized to receive Atozet® 10/20 mg or atorvastatin 40 mg. The primary endpoint was the mean percentage change from baseline LDL-C. Secondary endpoints included percentage of patients achieving LDL-C <2.6 mmol/L (<100.5 mg/dL) and the percentage change from baseline to 6 weeks in TC, TG, HDL-C, non-HDL-C, apo B and high-sensitivity C-reactive protein.

Reference: 1. Conard, S.E. et al. Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) versus up-titration of atorvastatin (to 40 mg) in hypercholesterolemic patients at moderately high risk for coronary heart disease. American Journal of Cardiology. 2008;102(11):1469-1494.

**Selected Safety Information of ATOZET®:** Indications: Prevention of Cardiovascular Events: ATOZET is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not. HYPERCHOLESTEROLAEMIA ATOZET is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate. Patients not appropriately controlled with a statin alone - patients already treated with a statin and ezetimibe. HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLAEMIA (HOFH) ATOZET is indicated as adjunctive therapy to diet for use in adults with HOFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein (LDL) apheresis). CONTRAINDICATIONS: - Hypersensitivity to the active substances or to any of the excipients. - Therapy with ATOZET is contraindicated during pregnancy and breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures. - ATOZET is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases exceeding 3 times the upper limit of normal (ULN). - ATOZET is contraindicated in patients treated with the hepatitis C antiviral glecaprevir/pibrentasvir. PRECAUTIONS: Myopathy/Rhabdomyolysis: In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. Rhabdomyolysis has been reported very rarely with ezetimibe monotherapy. Also, ATOZET contains atorvastatin, which is a HMG-CoA reductase inhibitor. Atorvastatin may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis. A CPK level should be measured before starting treatment. If CPK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started. Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing ATOZET. Liver Enzymes: Liver function tests should be performed before the initiation of treatment and periodically thereafter. Should an increase in transaminases of greater than 3 times the ULN persist, reduction of dose or withdrawal of ATOZET is recommended. Hepatic Insufficiency: Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ATOZET is not recommended. Interstitial lung disease: If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued. Diabetes mellitus: Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI >30kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. Excipients: ATOZET contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine. ADVERSE EVENTS: Common adverse reactions (≥1/100, <1/10) include diarrhoea and myalgia. In controlled clinical trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was 0.6% for patients treated with ATOZET. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline spontaneously or after discontinuation of therapy. Please consult the full prescribing information for detailed adverse events. Before prescribing, please consult the full prescribing information.

For healthcare professionals only

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SC-ATC-110019 Jun/2025

# Hope in Motion: Clinical Progress and Social Support for Parkinson's

Parkinson's disease (PD) remains an incurable neurological disorder that disproportionately affects the aging population, profoundly impacting patients and their families. In pursuit of better management strategies, extensive research and clinical trials are underway. Many of these efforts have yielded promising breakthroughs that offer hope for improving quality of life, despite the limited understanding of PD's underlying aetiology.

This article highlights recent advances in PD management, including novel therapeutic approaches such as  $\alpha$ -synuclein-targeted treatments, induced pluripotent stem cell replacement therapy, drug repurposing, deep brain stimulation, and non-pharmacological interventions. While much of this research is still in progress, these developments provide an encouraging outlook for the future of PD treatment and underscore the need for sustained, large-scale, and rigorous investigation to move beyond the current status quo.

## Introduction

Parkinson's Disease (PD) is a progressively deteriorating neurological disorder. PD most commonly affects populations over the age of 60, while it is comparatively less prevalent in younger populations.<sup>1,2</sup> The disease is characterised by motor symptoms such as tremors, bradykinesia, poor balance and posture, speech changes, muscle stiffness; and non-motor symptoms such as depression, anxiety, and sleep disturbance, among others.<sup>1-3</sup> In 2021 the prevalent cases of PD reached 11,767,271.97, suggesting a 2.74-fold increase in the number of cases compared to that in 1990.<sup>4</sup> The situation is even more dire in China: the estimated prevalence rose from 66.3 per 100,000 people in 1990 to 240.8 in 2023 (**Figure 1**).<sup>5</sup> Symptoms of PD are caused by a loss of dopaminergic neurons, primarily in the substantia nigra pars compacta.<sup>2,6</sup> A number of mechanisms have been proposed for the pathogenesis of PD, ranging from the formation of misfolded  $\alpha$ -synuclein and protein aggregation, malfunctions in the protein clearance system, to dysfunctional mitochondria.<sup>6</sup> Despite extensive efforts to elucidate its underlying causes, the aetiology of PD remains unclear.

Nevertheless, these ongoing research efforts have led to significant recent advances in its management.

## Treatments Targeting $\alpha$ -Synuclein

As aforementioned,  $\alpha$ -synuclein is critical in PD development. Encoded by the SNCA gene,  $\alpha$ -synuclein exists natively as an aqueous-soluble, unfolded protein without a rigid tertiary conformation.<sup>6,7</sup> The natively unfolded  $\alpha$ -synuclein monomer undergoes a significant structural transition to an  $\alpha$ -helical conformation upon interacting with negatively charged lipids or pre-existing  $\beta$ -sheet-rich structures (such as oligomers or fibrils).<sup>6,7</sup> The aggregation of  $\alpha$ -synuclein monomers into protofibrils and oligomers is a critical step in the pathogenesis of PD.<sup>7</sup> These prefibrillar intermediates are considered highly neurotoxic, causing cellular dysfunction before eventually maturing into insoluble fibrils that make up Lewy bodies (LB).<sup>7</sup> LBs are central to both PD and Lewy body dementia, and they can also overlap with Alzheimer's disease (AD).<sup>8</sup> Therefore, targeting and reducing  $\alpha$ -synuclein formation is the most heavily pursued disease-modifying strategy in PD.<sup>9</sup>



### Reducing $\alpha$ -Synuclein

Recent research targeting  $\alpha$ -synuclein has demonstrated potential disease-modifying effects. One such example is buntanetap, which acts by reducing  $\alpha$ -synuclein production in neurons.<sup>9</sup> Buntanetap is a small molecule that blocks the translation of mRNAs into proteins (including  $\alpha$ -synuclein) specifically in diseased cells.<sup>10</sup> In a study involving 53 patients with early PD and 14 patients with AD over a  $25 \pm 2$  day period, Fang et al. demonstrated that buntanetap's rapid effects support its potential as a symptomatic treatment, while also hypothesising that it may possess long-term disease-modifying properties for PD.<sup>10</sup> However, the treatment effect is only nominally significant.<sup>11</sup> Currently, a phase III trial is underway to ascertain buntanetap's long-term effects (NCT06709014).<sup>11</sup>

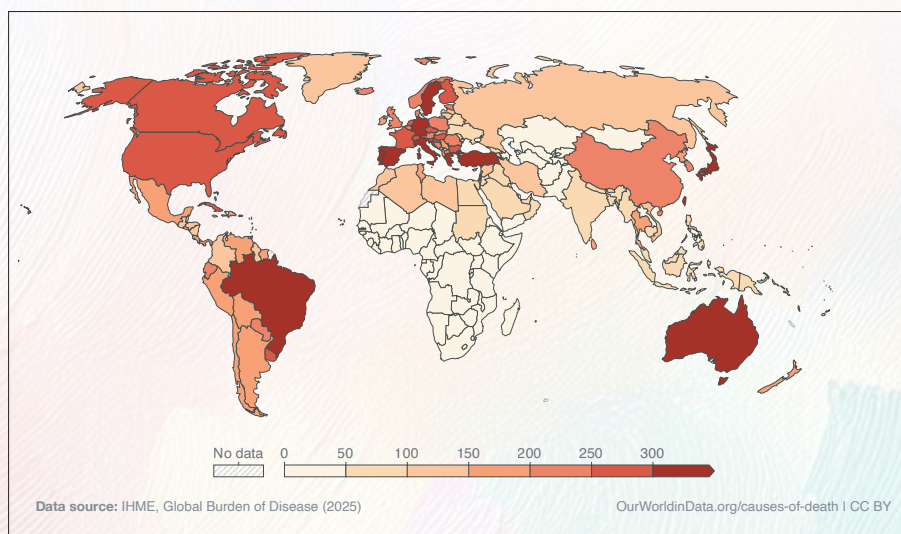
### Preventing $\alpha$ -Synuclein Propagation

Another example of an  $\alpha$ -synuclein-targeting therapy is prasinezumab, the first monoclonal antibody designed to bind  $\alpha$ -synuclein aggregates and inhibit their intercellular propagation.<sup>12</sup> Although in the PASADENA phase 2 study, prasinezumab did not demonstrate significant effects in Parts I and II of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), it was associated with a slowing of motor function decline in Part III.<sup>12</sup> An exploratory analysis of PASADENA might suggest that prasinezumab slows the progression of motor signs in individuals with characteristics usually associated with more rapid progression within a 1-year

timeframe.<sup>12</sup> To this end, PADOVA, a larger-scaled clinical trial, is underway (NCT04777331).<sup>13,14</sup>

### Targeting $\alpha$ -Synuclein with Vaccines

A proposed way to neutralise  $\alpha$ -synuclein is through immunotherapy. PD01A and PD03A vaccines represent the first active immunotherapies developed to target the C-terminal region of the  $\alpha$ -synuclein protein.<sup>15,16</sup> To produce the vaccines, the antigenic peptides PD01 and PD03 are conjugated to keyhole limpet hemocyanin and adsorbed onto aluminium hydroxide.<sup>15,16</sup> These vaccine designs utilise antigenic B-cell epitopes to stimulate the production of anti- $\alpha$ -synuclein antibodies, while relying on the conjugated carrier protein to provide foreign helper T-cell epitopes for sustained antibody production without triggering auto-reactive T-cell responses.<sup>15,16</sup> In both phase I studies, the vaccines were safe and well-tolerated, with significant humoral immunity against  $\alpha$ -synuclein ( $n=21$  for PD01A;  $n=36$  for PD03A).<sup>15,16</sup> The immunogenicity of PD01A was higher than that of



**Figure 1.** Estimated worldwide Parkinson's Disease prevalence 2023 (per 100,000 people)<sup>5</sup>

PD03A.<sup>16</sup> However, the therapeutic efficacies of these vaccines have not been studied and are the central focus of coming phase II research.<sup>15,16</sup>

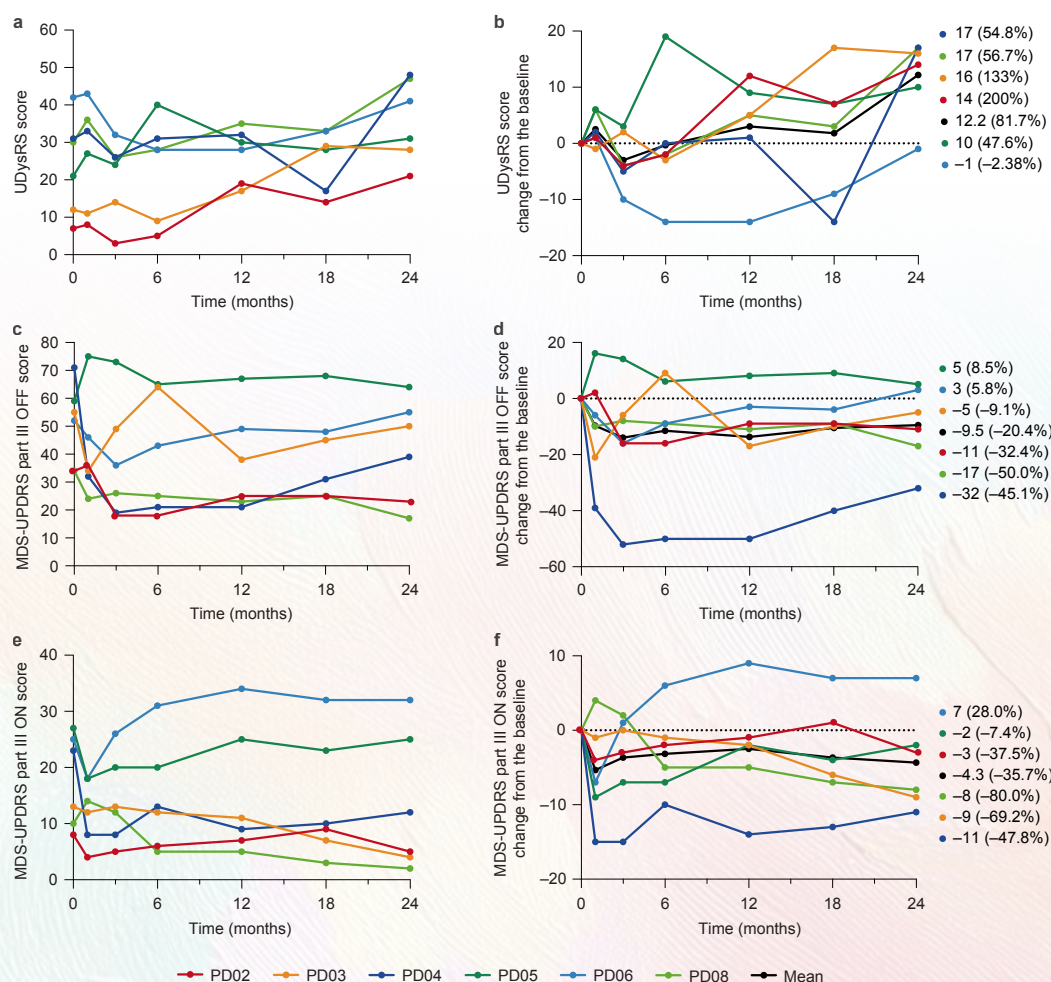
### Induced Pluripotent Stem Cell Therapy for PD

As is well known, PD symptoms primarily originate from the loss of dopaminergic neurons in the substantia nigra pars compacta region. Replenishing dopaminergic neurons has long been pursued as a therapeutic strategy for PD, with efforts dating back as early as 1989.<sup>17</sup> Yet, owing to technological limitations and ethical concerns regarding the use of human embryonic stem cells for the said purpose, researching cell replacement therapies for PD has been arduous.<sup>17</sup> The advent of induced pluripotent stem cell (iPSC) technology has significantly advanced research into cell replacement therapies for PD.<sup>17</sup> Notably, Japan completed a phase I/II clinical trial of iPSC-derived dopaminergic cells for PD in 2025.<sup>18</sup>

While iPSCs have facilitated progress in developing cell replacement therapies for PD, the process remains highly complex and challenging. The iPSC cells were obtained from an established master cell bank and were then subjected to neural induction via SMAD

inhibition and floor plate induction protocol.<sup>19,20</sup> Yet the importance of cell sorting and quality control must be underscored—as the undesirable cells may limit treatment efficacy or even exacerbate dyskinesia, and worse still, form tumours.<sup>20</sup> Using Fluorescence-Activated Cell Sorting (FACS) to isolate CORIN+ cells is a well-established strategy to enrich midbrain dopaminergic (mDA) progenitors.<sup>20</sup> Following transplantation into hemi-parkinsonian rat models, these sorted populations exhibited robust post-graft survival, integrated functionally into the host striatum, and induced significant, quantifiable improvements in motor behaviour.<sup>20</sup> Using the method described above, the iPSC-derived dopaminergic progenitors were prepared for the transplantation in the clinical trial.<sup>18</sup>

The encouraging results from Sawamoto et al.'s trial demonstrated both the safety and efficacy of cell replacement therapy for PD using iPSC-derived dopaminergic progenitors. Over the two years following bilateral transplantation in 7 patients (PD01-06, PD08) included in the safety analysis, no serious adverse events were reported. The adverse events that did occur were largely transient and unlikely to be attributable to the transplanted cells. Furthermore, magnetic



**Figure 2.** Chronological changes in clinical end points.<sup>18</sup> MDS-UPDRS: Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; UDysRS: Unified Dyskinesia Rating Scale

resonance imaging revealed no evidence of tumour formation or growth. The efficacy of the treatment was further investigated in 6 of the 7 patients, excluding the patient with unilateral transplants performed separately (PD01). The Unified Dyskinesia Rating Scale (UDysRS) total scores improved in 5 of the 6 patients over 24 months, with an average increase of 12.3 points from baseline. As another secondary endpoint, treatment efficacy was assessed using the MDS-UPDRS Part III. Surprisingly, 4 of the 6 eligible patients demonstrated improved motor function during the off-time period (more than 12 hours without medication), while 5 of the 6 showed improvement during the on-time period (with medication). The combined MDS-UPDRS Parts I + II + III (OFF) revealed a modest average improvement of -3.1 points over 24 months.<sup>18</sup> These findings suggest that cell replacement therapy may confer therapeutic benefits in addition to demonstrating a favourable safety profile (**Figure 2**). As noted in the study, future investigations that are double-blinded, placebo-controlled, and conducted with larger sample sizes may address its limitations and provide further benefits to the development of cell replacement therapy.<sup>18</sup>

### Drug Repurposing for PD

Glucagon-like peptide-1 receptor (GLP-1R) agonists, widely used in diabetes treatment, may potentially be beneficial to PD treatment. Meta-analyses and reviews have indicated that treatment with GLP-1R agonists may enhance both motor and cognitive functions in PD patients.<sup>21,22</sup> The neuroprotective effects of GLP-1R agonists such as exendin-4 and liraglutide have been well documented in mouse models.<sup>20</sup> In addition to preclinical evidence supporting the benefits of GLP-1R agonists in PD, clinical trials have also demonstrated that these agents can produce favourable outcomes.<sup>21,22</sup>

In a meta-analysis of five eligible studies comprising 484 patients, in the off-medication state, GLP-1R agonists improved the MDS-UPDRS Part III score by -1.22 points compared to placebo (95% confidence interval [CI] -2.46, 0.22;  $P = 0.05$ ); and in the on-medication state, there was a -2.52 point improvement (95% CI -4.02, -1.01;  $P = 0.001$ ).<sup>22</sup> In addition, cognitive performance, assessed via the Mattis Dementia Rating Scale-2 (MATTIS-DRS2), improved by 1.32 points (95% CI 0.16, 2.52;  $P = 0.03$ ).<sup>22</sup> These improvements may stem from the anti-inflammatory properties of GLP-1R agonists, their capacity to reduce oxidative stress and protein misfolding, and their ability to promote autophagy.<sup>21</sup> These data showed that GLP-1 receptor agonists improved motor and

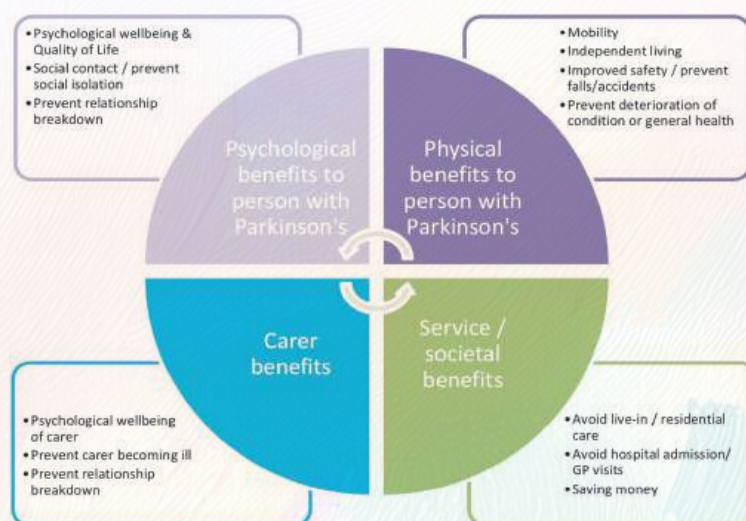
cognitive performance in PD, suggesting potential symptomatic benefits. However, further studies are needed to evaluate their long-term effects and their role in disease modification.<sup>22</sup>

### Deep Brain Stimulation (DBS)

Deep brain stimulation (DBS) is a highly effective surgical treatment for managing PD, typically considered when medication and other therapeutic options are no longer sufficient. The procedure involves implanting electrodes into specific brain regions—such as the globus pallidus internus (GPi), subthalamic nucleus (STN), and ventral intermediate nucleus (VIM)—which are then connected to a pacemaker-like device that delivers electrical impulses to modulate neural activity.<sup>23,24</sup> Each targeted region serves distinct functions, and stimulation should be tailored to the patient's individual therapeutic goals.<sup>24</sup> Future research on DBS may explore its potential disease-modifying effects, novel stimulation targets, multi-target approaches, and the integration of artificial intelligence into adaptive DBS systems.<sup>25,26</sup>

### Non-pharmacological Support for PD Patients

Beyond medical advances in PD treatment, equal attention must be given to societal care, non-pharmacological interventions, psychological support, and caregiver assistance. A qualitative collective case study conducted in Northern and Midland regions of England examined the impact of societal care interventions.<sup>27</sup> The findings indicated that effective societal care yields a wide range of interconnected benefits—physical, psychological, social, and service-related—as illustrated in **Figure 3**.<sup>27</sup>



**Figure 3.** Benefits of social care.<sup>27</sup> GP: general practitioner

Notably, the study highlighted the role of timely, high-quality societal care in mitigating the overall cost burden associated with managing PD.<sup>27</sup> Physical non-pharmacological interventions—such as dietary modification and structured exercise—have also demonstrated clear benefits in disease management. In addition to physical improvements, exercise has been shown to enhance cognitive function and mental well-being,<sup>28</sup> and to slow the decline in postural control and gait stability among PD patients.<sup>29</sup> Dietary patterns, including adherence to a Mediterranean diet, consumption of unprocessed foods, and moderate coffee intake, have similarly been associated with slower disease progression.<sup>29</sup> These findings are particularly significant given that pharmacological treatments, despite their widespread use and potential side effects, often have limited impact on maintaining or improving mental health.<sup>28</sup> However, the evidence base supporting non-pharmacological interventions remains limited, largely due to challenges inherent in studying lifestyle-based approaches. Furthermore, public awareness of PD continues to be inadequate, as noted in the study by Tod et al.<sup>27</sup>

In Hong Kong, there are a limited number of organisations that provide support for patients with PD. Notably, the Hong Kong Parkinson's Disease Foundation offers a range of services to patients and

their caregivers, including day care programmes, transportation services, and a personal emergency link service.<sup>30</sup> Additionally, a range of resources are available, including information on treatment options, caregiving advice, publications on the foundation's activities, updates on PD, and recreational programmes such as table tennis competitions and Tai Chi classes.<sup>30</sup> The Elderly Health Service under the Department of Health also provides information and guidance on caring for individuals with PD.<sup>31</sup>

## Conclusion

PD is a progressive neurological disorder caused by the loss of dopamine-producing neurons, leading to motor and non-motor symptoms. Although it is currently incurable, recent advances aim to improve management and slow disease progression. New treatments focus on targeting  $\alpha$ -synuclein, a key protein in PD, through drugs, antibodies, and vaccines. Stem cell therapy has also shown promise in replacing damaged neurons, while diabetes drugs (GLP-1 agonists) may improve symptoms. Deep brain stimulation remains an effective option for advanced cases. In addition, lifestyle changes, exercise, and social support are important in improving patients' quality of life. Overall, these developments offer hope for better treatment and future breakthroughs.



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# Advancing Schizophrenia Care with INTEGRATE: Practical, Global, Algorithm-based Guidance

At a recent webinar, Professor Dan Siskind, Professor of Psychiatry at the University of Queensland, Brisbane, Australia, presented key recommendations from the International College of Neuropsychopharmacology (CINP)-endorsed International Guidelines for the Algorithmic Treatment of Schizophrenia (INTEGRATE).

## INTEGRATE: Global, concise, and algorithm-based guidance

While clinical guidelines for schizophrenia treatment, such as those from the National Institute for Health and Care Excellence (NICE) and the American Psychiatric Association (APA), are available, they are often lengthy, predominantly country-specific rather than global, and not algorithm-based. INTEGRATE provides concise, internationally adaptable, algorithmic, evidence-based recommendations (**Diagram 1**).<sup>1</sup> These recommendations were developed through an umbrella review of the literature, input from expert workshops, and a consensus survey of 70 international schizophrenia experts across 30 countries.<sup>1</sup>

## First-episode psychosis: When to start treatment?

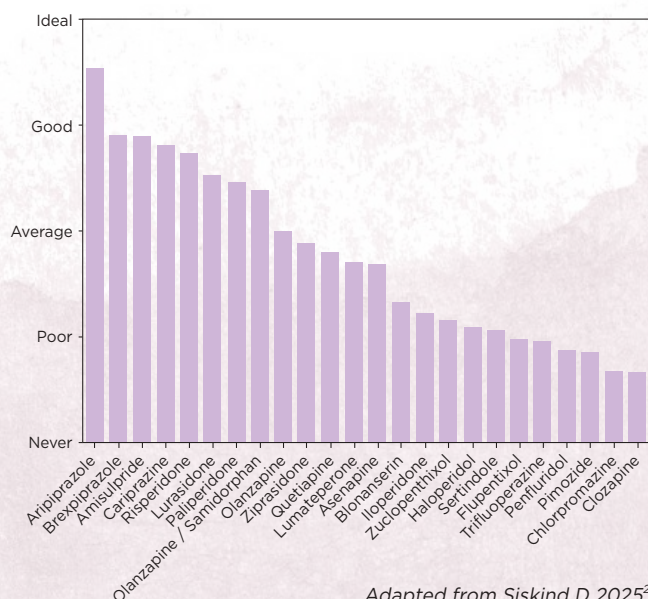
Within the INTEGRATE framework, first-episode psychosis management begins with shared decision-making regarding treatment initiation and antipsychotic selection.<sup>1</sup> Antipsychotic treatment may need to begin at the initial presentation, even before schizophrenia is definitively diagnosed.<sup>1</sup> As a general principle, treatment should be offered when psychotic symptoms have persisted for a week or more and are associated with distress or functional impairment, although earlier initiation is appropriate when distress is severe or there are safety risks to the patient or others.<sup>1</sup> This staged approach balances timely symptom control with prudent diagnostic clarification.

## First-episode psychosis: What to choose?

Antipsychotic selection is best based on comparative efficacy and side-effect profiles, alongside consideration of dose scheduling, convenience, and the availability of long-acting formulations.<sup>1</sup> In the absence of preference, agents with a lower overall adverse-effect burden, such as dopamine D2-receptor partial agonists (for example, aripiprazole), are recommended as first-line antipsychotics, and prolactin-raising drugs should be avoided where possible, particularly in women of childbearing potential (**Figure 1**).<sup>1,2</sup> If agents with higher metabolic liability (for example, olanzapine or clozapine) are used, concurrent lifestyle modification, an antipsychotic switch and metformin should be offered to mitigate weight gain (**Diagram 1**).<sup>1</sup> In practice, these considerations help individualise therapy while anticipating and minimising long term cardiometabolic risks.

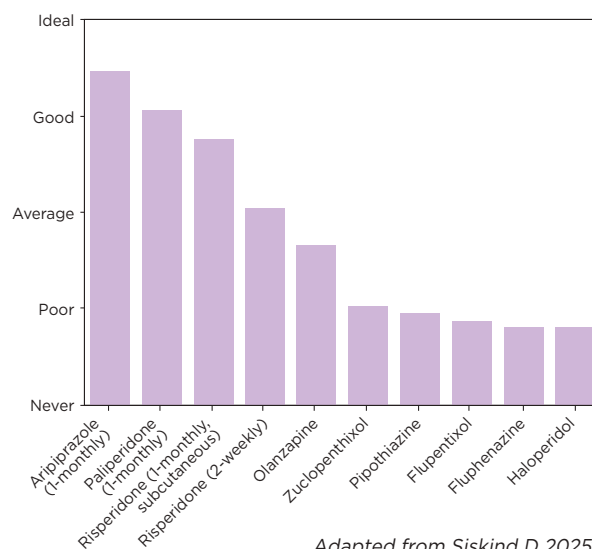
## Addressing treatment adherence in schizophrenia

Adherence should be addressed proactively from treatment initiation and reviewed regularly, especially in cases of non-response or partial response.<sup>1</sup> Beyond patient self-report, objective measures should be employed, including plasma antipsychotic concentrations where feasible.<sup>1</sup> Low plasma levels often indicate recent non-adherence, although rapid metabolism or impaired absorption must be considered.<sup>1</sup> When estimated adherence falls below approximately 80% of the prescribed dose, clinicians should discuss



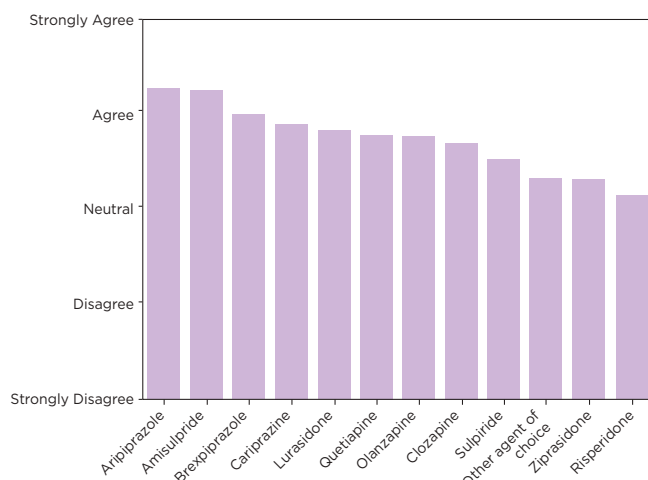
Adapted from Siskind D 2025<sup>2</sup>

the option of long acting injectable (LAI) formulations, such as aripiprazole once-monthly (**Figure 2**).<sup>1,2</sup> Given the difficulty of detecting non-adherence, it might be reasonable to consider LAIs even without overt evidence of non-adherence, particularly in non-response or partial response, with selection guided by side effect profiles and shared decision making.<sup>1</sup> Thus, systematic assessment and early recourse to LAIs can be pivotal in optimising outcomes.



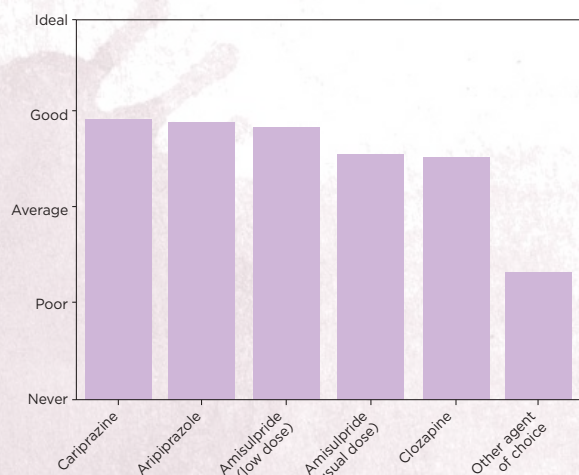
Adapted from Siskind D 2025<sup>2</sup>

**Figure 2:** Preferred long acting injectable in schizophrenia, based on a survey of a working group with 70 respondents from 30 countries.<sup>2</sup>



Adapted from Siskind D 2025<sup>2</sup>

**Figure 3:** Preferred antipsychotic agents for managing depressive symptoms in schizophrenia, based on a survey of a working group with 70 respondents from 30 countries.<sup>2</sup>



Adapted from Siskind D 2025<sup>2</sup>

**Figure 4:** Preferred antipsychotic agents for managing negative symptoms in schizophrenia, based on a survey of a working group with 70 respondents from 30 countries.<sup>2</sup>

### Addressing depressive symptoms in schizophrenia

In individuals with schizophrenia who present with depressive symptoms, both evidence-based psychological therapies for depression and antidepressant pharmacotherapy should be considered.<sup>1</sup> At present, evidence does not support the superiority of any single antidepressant for depression in this population; therefore, treatment selection should follow a shared decision-making approach informed by comparative side-effect profiles and patient preferences.<sup>1</sup> Where a change in antipsychotic treatment is clinically indicated, switching to a D2-receptor partial agonist such as aripiprazole or amisulpride is a suitable strategy (**Figure 3**).<sup>1,2</sup> Clinicians should also evaluate whether apparent depressive features are partly attributable to negative symptoms and, where appropriate, implement targeted measures such as cautious antipsychotic dose reduction.<sup>1</sup> Integrating these steps ensures that depressive symptoms are addressed holistically and proportionately.

### Addressing negative symptoms in schizophrenia

For persistent negative symptoms in schizophrenia, potential reversible secondary contributors should first be identified and addressed.<sup>1</sup> These include ongoing positive symptoms, depressive symptoms, substance misuse, social isolation, medical comorbidities, and antipsychotic adverse effects.<sup>1</sup> Psychosocial interventions may be offered to mitigate maintaining

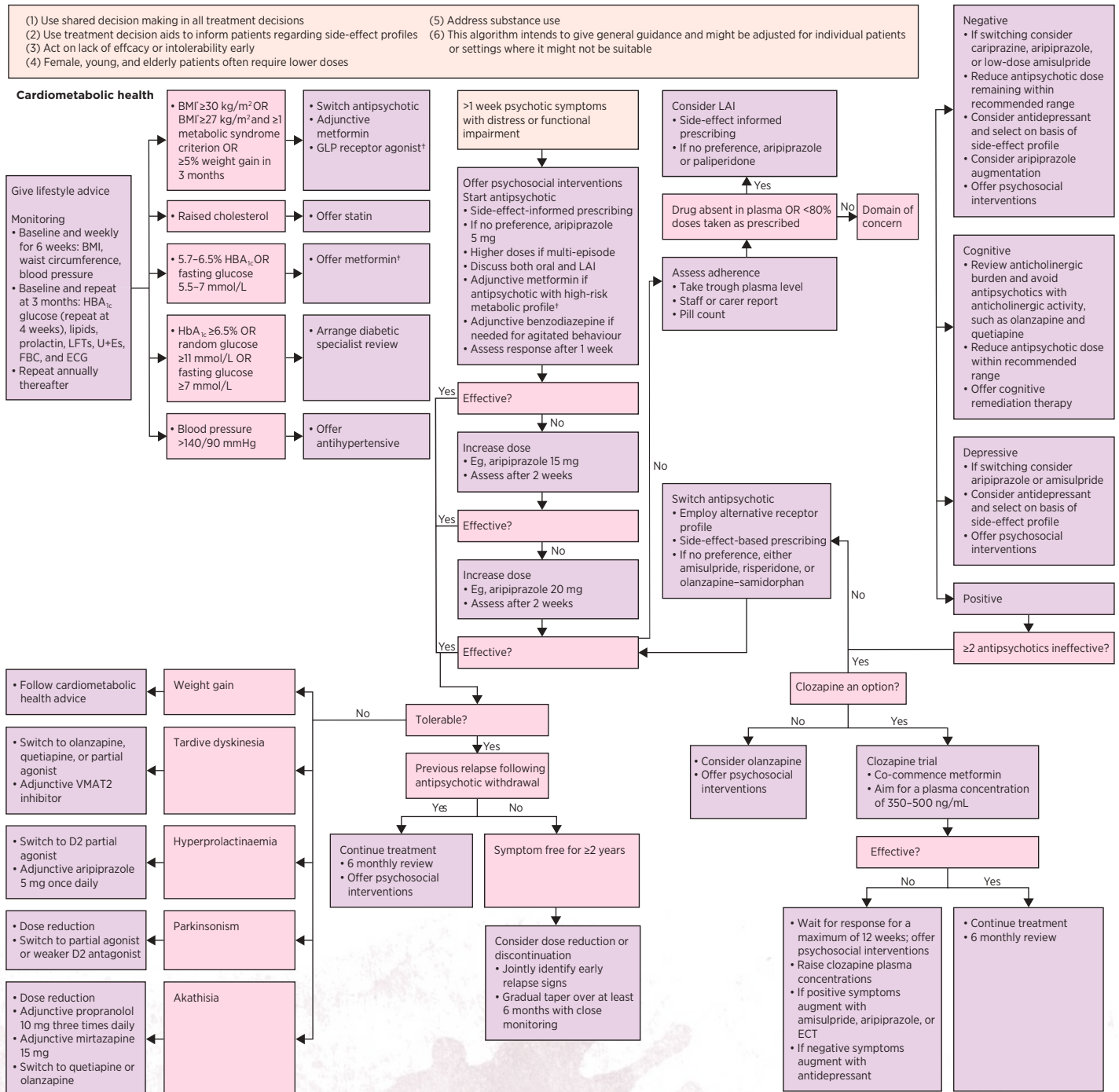
psychological factors and promote social engagement.<sup>1</sup> Where positive symptoms are well controlled, a cautious, gradual reduction of antipsychotic dose within the therapeutic range may be considered.<sup>1</sup> If switching is indicated, cariprazine or aripiprazole are suitable options; low-dose amisulpride may be considered when negative symptoms predominate and positive symptoms are not a concern (**Figure 4**).<sup>1,2</sup> Adjunctive antidepressants (even without formal depression) and aripiprazole augmentation may be trialled, with clear risk-benefit discussion and shared decision-making guided by side-effect profiles.<sup>1</sup>

### Conclusion

In summary, INTEGRATE offers a concise, internationally applicable, and algorithm driven framework that enhances the consistency and timeliness of schizophrenia care.<sup>1</sup> By emphasising shared decision making, early yet judicious initiation of antipsychotics, rational agent selection with proactive metabolic risk mitigation, and structured adherence management including the considered use of LAIs, the guidance supports personalised, evidence based practice.<sup>1</sup> Its recommendations on managing comorbid depressive symptoms further strengthen comprehensive care, positioning INTEGRATE as a practical tool for clinicians across varied health care contexts.

### Take-home messages

- **INTEGRATE:** Offers concise, globally adaptable, evidence based, **algorithm based recommendations for treatment of schizophrenia**, developed via an umbrella literature review, expert workshops, and a consensus survey of 70 international schizophrenia experts across 30 countries.<sup>1</sup>
- Antipsychotic treatment may be initiated at first presentation, even before a definitive diagnosis of schizophrenia, and is generally recommended after **more than one week** of psychotic symptoms causing distress or functional impairment, or earlier when severe distress or safety risks are present.<sup>1</sup>
- When estimated adherence falls below approximately 80% of the prescribed dose, **LAI formulations, such as once-monthly aripiprazole**, should be considered.<sup>1</sup>
- In the absence of therapeutic preference, antipsychotic agents with a comparatively lower overall adverse-effect burden, such as **dopamine D2-receptor partial agonists (for example, aripiprazole)**, are recommended as **first-line antipsychotics**.<sup>1</sup>
- In schizophrenia with depressive symptoms, switching to a **dopamine D2-receptor partial agonist** may be considered where clinically indicated, alongside evidence-based psychological therapy.<sup>1</sup>
- For persistent negative symptoms, if switching is indicated, **cariprazine or aripiprazole** are suitable options; low-dose amisulpride may be considered when negative symptoms predominate and positive symptoms are not a concern.<sup>1</sup>

Adapted from McCutcheon RA, et al 2025<sup>1</sup>**Diagram 1:** Algorithmic summary of treatment guidelines for schizophrenia.<sup>1</sup>

HbA<sub>1c</sub>=haemoglobin A<sub>1c</sub>. LFT=liver function test. U+E=urea and electrolyte. FBC=full blood count. ECG=electrocardiogram. VMAT2=vesicular monoamine transporter 2. LAI=long-acting injectable. ECT=electroconvulsive therapy. \*Lower BMI thresholds by 2.5 kg/m<sup>2</sup> for people from South Asian, Chinese, other Asian, Middle Eastern, Hispanic, Black African, or African-Caribbean family backgrounds. <sup>†</sup>When using metformin start at 500 mg once per day, aim for minimum of 1 g once per day and maximum of 1 g twice per day. Check B12 concentrations annually.

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# Advances in the Management of Marginal Zone Lymphoma with Zanubrutinib



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Despite the typically indolent nature of marginal zone lymphoma (MZL), treatment options for patients with relapsed or refractory (R/R) disease have long been limited and largely extrapolated from broader indolent non-Hodgkin lymphoma studies. Conventional chemoimmunotherapy, though effective, can be poorly tolerated in older or comorbid patients, while first-generation Bruton tyrosine kinase (BTK) inhibitors like ibrutinib have been associated with off-target toxicities. This created a critical therapeutic gap for patients requiring prolonged treatment with manageable safety profiles. Zanubrutinib, a next-generation BTK inhibitor engineered for greater target selectivity and improved tolerability, has emerged as a promising solution. At a recent symposium, Dr. Chandramouli Nagarajan presented the findings of the MAGNOLIA trial, a pivotal phase II study that evaluated Zanubrutinib as monotherapy in patients with R/R MZL. By focusing on a real-world population, including elderly patients, the study offers compelling evidence for the role of Zanubrutinib in reshaping the treatment landscape of MZL.

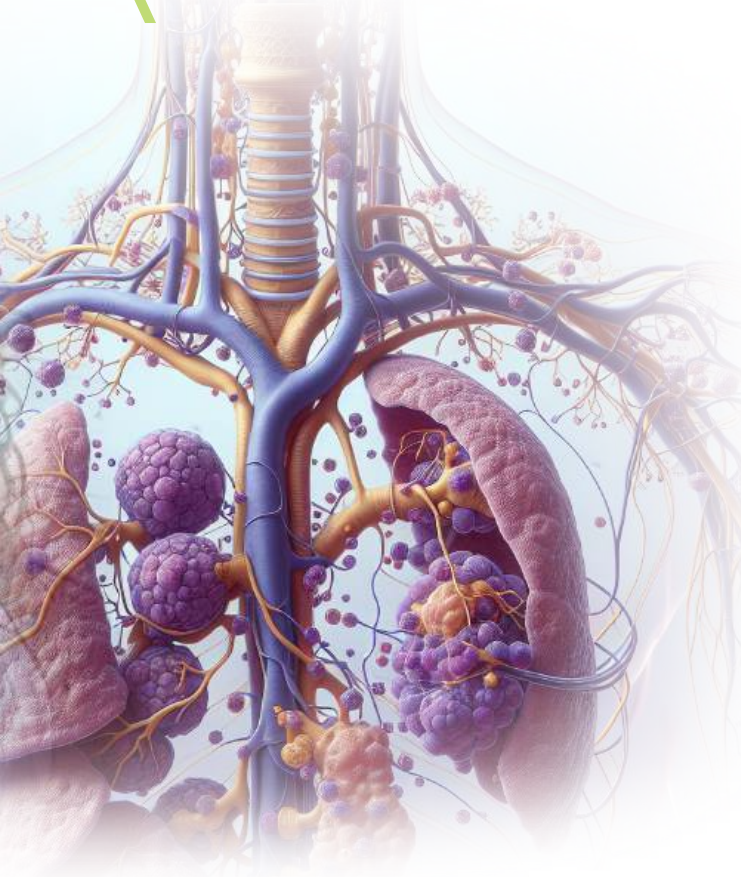
## ■ Marginal Zone Lymphoma and the Common Subtypes

MZL arises from memory B cells located in the marginal zones of secondary lymphoid tissues. It accounts for approximately 7-10% of all B-cell NHLs and comprises three main subtypes, each with distinct clinical features, pathogenesis, and therapeutic considerations<sup>1</sup>.

The most common subtype is extranodal MZL, often referred to as mucosa-associated lymphoid tissue (MALT) lymphoma. This form primarily affects the stomach but can also arise in other mucosal sites such as the lungs, conjunctiva and skin<sup>1</sup>. Chronic antigenic stimulation from infections is a key driver of this

lymphoma. For instance, *Helicobacter pylori* infection is strongly associated with gastric MALT lymphoma, while *Chlamydia psittaci* and *Borrelia burgdorferi* are implicated in ocular and cutaneous forms, respectively<sup>1</sup>. These lymphomas tend to exhibit indolent behavior and may initially be managed with a "watch and wait" approach<sup>2</sup>. In many cases, addressing the underlying infection is sufficient. However, patients with gastric MALT lymphoma who have the t(11;18) translocation may require gastric irradiation, while those with more disseminated diseases, typically Stage III or IV, generally need systemic therapy that includes CD20-based immunochemotherapy<sup>2</sup>.

Splenic MZL, the second most common subtype, presents with splenomegaly, bone marrow involvement,



and cytopenias<sup>12</sup>. It is occasionally linked to hepatitis C virus (HCV) infection, where antiviral therapy alone may be effective<sup>12</sup>. Historically managed with splenectomy, current treatment strategies now often favor systemic approaches<sup>3</sup>. The nodal MZL is relatively rare, which typically involves generalized lymphadenopathy and is often presented at advanced stage<sup>3</sup>. It requires systemic treatment similar to that used for follicular lymphoma<sup>3</sup>.

### Pathogenesis and Target Therapy

In discussing the molecular biology of MZL, Dr. Nagarajan emphasized the central role of B-cell receptor (BCR) signaling in the pathogenesis of the disease. He noted that two major therapeutic targets have emerged from this understanding: BTK, which is critical in BCR pathway signaling<sup>4</sup>, and phosphoinositide 3-kinase (PI3K), which is involved in cellular proliferation and survival<sup>5</sup>. Zanubrutinib, a more selective BTK inhibitor, was developed to overcome the off-target toxicities of ibrutinib, such as atrial fibrillation and bleeding, while delivering deeper, more durable responses with improved safety<sup>4</sup>.

### Outline of the MAGNOLIA Trial

The MAGNOLIA trial was a pivotal phase II, open-label, single-arm, multicenter study investigating the efficacy and safety of Zanubrutinib in patients with relapsed or refractory MZL<sup>4</sup>. Remarkably, the MAGNOLIA trial included a patient group that had received at least one prior CD20-directed therapy yet remained in need of systemic treatment due to progression or relapse<sup>4,6</sup>.

As of mid-2024, a total of 68 patients were enrolled and treated in the MAGNOLIA study, with 66 patients evaluable for efficacy<sup>6</sup>. The median age of patients was 70 years, with 27.9% of them aged 75 or older, which aligned with the real-world clinical observation<sup>6</sup>. Among the patients enrolled, 38.2% had extranodal (primarily mucosa-associated lymphoid tissue), 38.2% had nodal, 17.6% had splenic MZL, and 5.9% had an unknown subtype. 89.7% of the patients presented with FDG-avid disease as assessed by an independent review committee (IRC)<sup>6</sup>.

Regarding prior treatment, most had previously been treated with rituximab-based regimens, including BR (bendamustine-rituximab) and R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone). Nonetheless, 32.4% of patients treated with chemoimmunotherapy (CIT) developed refractory disease<sup>4,6</sup>.

The patients were provided with oral Zanubrutinib, 160 mg twice daily, continued until disease progression or the emergence of unacceptable toxicity<sup>6</sup>. The primary endpoint of the study was the overall response rate (ORR), with additional endpoints related to durability and tolerability examined during longer-term follow-up as assessed by an IRC<sup>4,6</sup>.

### Promising Results Generated with Zanubrutinib

After a median follow-up of 15.7 months, Zanubrutinib yielded a robust ORR of 68.2%, with 25.8% of patients achieving a complete response (CR). Investigator-assessed ORR was slightly higher at 74.2%, with an identical CR rate of 25.8%, reinforcing the consistency and reliability of the responses (**Figure 1**)<sup>7</sup>. Responses were observed across all MZL subtypes, demonstrating

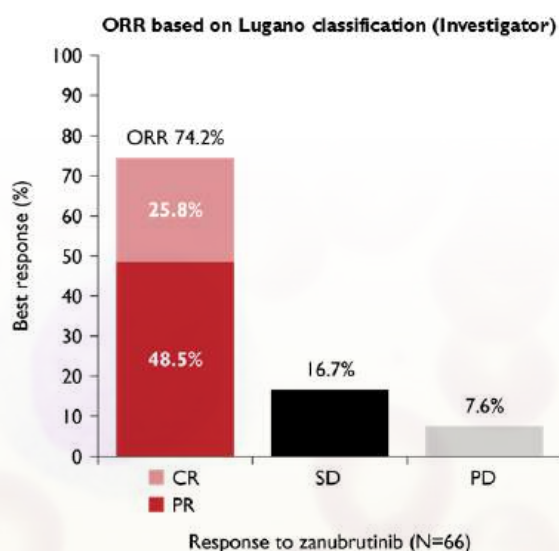
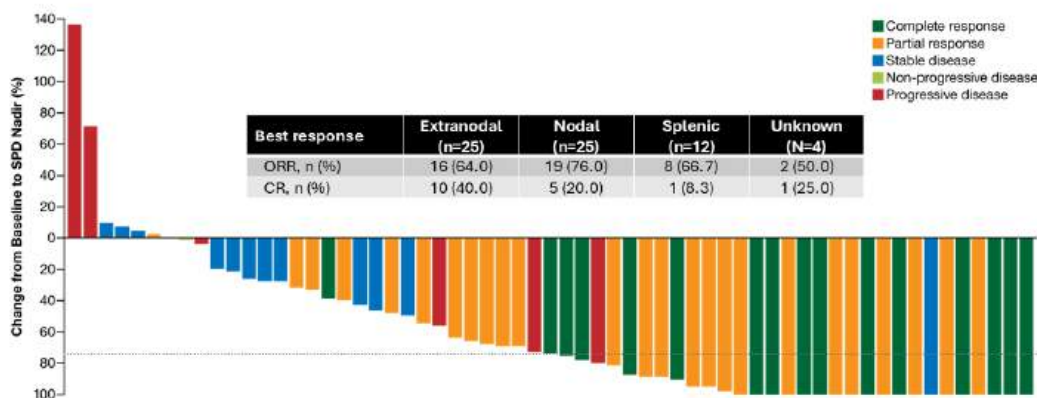


Figure 1: Overall Response by Investigator Assessment<sup>7</sup>

## MAGNOLIA



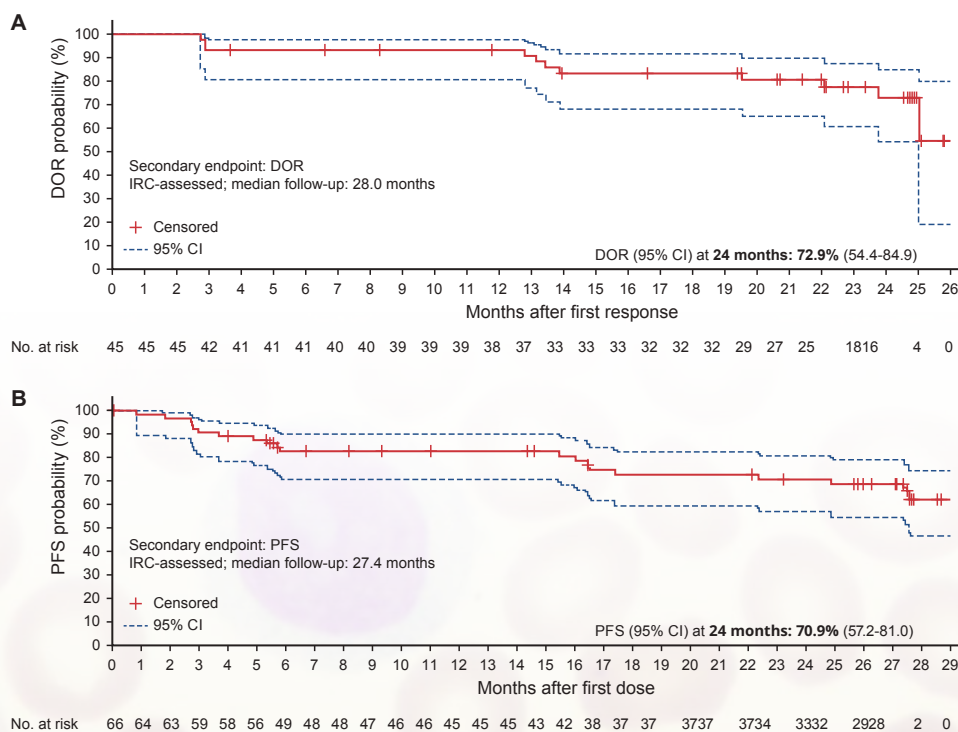
**Figure 2:** Change in Target Lesion SPD\* by IRC<sup>7</sup>  
 \*SPD = Sum of the Products of Perpendicular Diameters

the broad efficacy of Zanubrutinib. In extranodal MZL, the ORR was 64.0% with a notable CR rate of 40.0%. Nodal MZL demonstrated the highest ORR at 76.0%, though with a lower CR rate of 20.0%. In splenic MZL, the ORR was 66.7% with a CR rate of 8.3%, while patients with an unknown subtype showed an ORR of 50.0%, including a CR rate of 25.0% (**Figure 2**)<sup>7</sup>. These differences underscore the variation in disease biology between subtypes, but also highlight the consistent activity of Zanubrutinib regardless of presentation<sup>4,6,7</sup>.

Importantly, the durability of response was a defining feature of the study. At the 12-month mark, the IRC-assessed duration of response (DOR) rate was 93.0%, and the progression-free survival (PFS) rate was 82.5%,

where both sustained throughout 15 months<sup>7</sup>. Median DOR, PFS, and overall survival (OS) were not reached at the time of the most recent data cut-off, indicating a sustainable benefit for a large proportion of patients<sup>4</sup>. At the 2-year follow-up, over 70% of patients remained alive and progression-free, with survival curves demonstrating sustained disease control across all MZL subtypes (**Figure 3 A,B**)<sup>4</sup>.

The safety profile of Zanubrutinib was favorable and consistent with prior data in other B-cell malignancies. Most adverse events (AEs) were grade 1 or 2 while the most commonly reported treatment-emergent AEs were bruising (23.5%), diarrhea (22.1%), and constipation (17.6%)<sup>4,6</sup>. Grade 3 or higher AEs were



**Figure 3:** DOR (A) and PFS (B) of Patients at the Median Follow-up assessed by IRC<sup>4</sup>

uncommon; neutropenia occurred in 8.8% of patients, and COVID-19 pneumonia in 5.9%. Atrial fibrillation and atrial flutter were reported in 1.5% of patients, and grade 3 hypertension occurred in 2.9%. Treatment discontinuation occurred in 35.3% of patients due to disease progression and in 7.4% due to AEs, which investigators did not attribute directly to Zanubrutinib<sup>4</sup>. Importantly, there was only one (1.5%) report of grade 3 major hemorrhage. Five patients (7.4%) died during the study, all due to causes deemed unrelated to Zanubrutinib<sup>4</sup>. These included two deaths from COVID-19 pneumonia, one from acute myeloid leukemia (in a patient with prior alkylating agent exposure), one from myocardial infarction (in the setting of pre-existing coronary artery disease), and one from septic encephalopathy in a patient in complete remission<sup>6</sup>.

Although the study enrolled predominantly patients who were older with preexisting comorbidities, the incidence of cardiac events, including hypertension and arrhythmias, was low, with none leading to treatment withdrawal.<sup>4</sup>

Finally, an exploratory observation in the study highlighted the potential influence of MYD88 mutation status, commonly associated with Waldenström's macroglobulinemia<sup>8</sup>. Although patients harboring the MYD88 mutation appeared to derive enhanced benefit, those without the mutation also experienced strong responses, suggesting that the efficacy of Zanubrutinib is not strictly dependent on this molecular marker (Figure 4)<sup>8</sup>.

Taken together, the MAGNOLIA study results demonstrate that Zanubrutinib offers a high response rate, deep and durable remissions, and a favorable

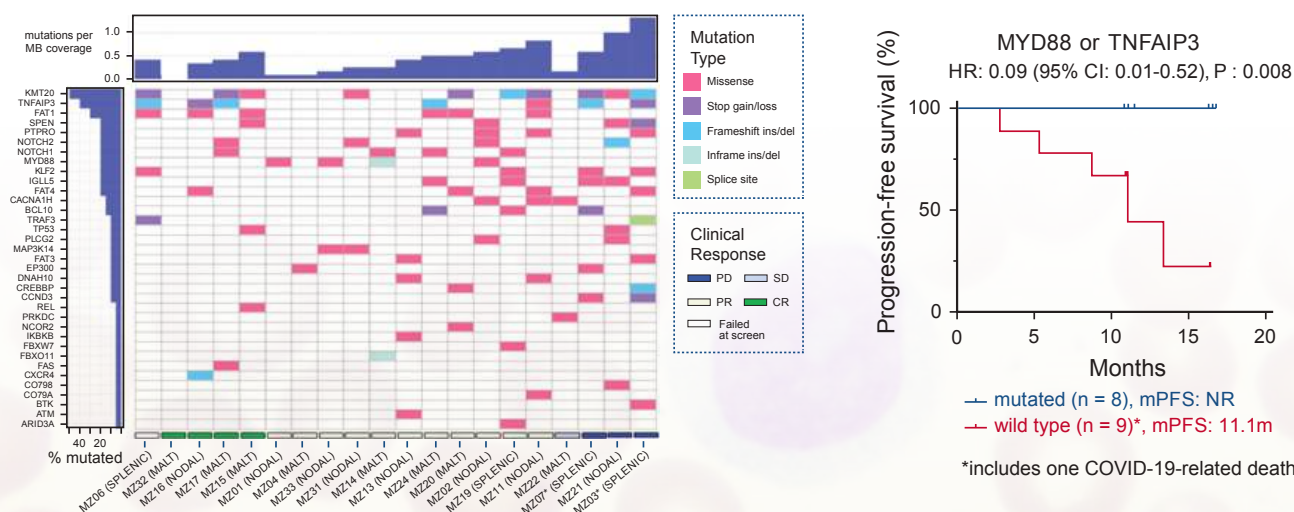
safety profile across MZL subtypes and patient age groups, affirming its role as an important therapeutic option in the R/R setting.

### Zanubrutinib in the Elderly: A Case Highlighting Efficacy and Safety

To illustrate the treatment outcomes of Zanubrutinib in older individuals, Dr. Nagarajan presented a case involving a 72-year-old man with multiple chronic conditions, including hypertension, hyperlipidemia, diverticular disease, benign prostatic hyperplasia, and chronic hepatitis B virus (HBV) carriage. The patient presented with abdominal pain, and imaging revealed retroperitoneal lymphadenopathy, fat stranding, and small-volume nodes above the diaphragm. A lymph node biopsy confirmed an indolent CD20-positive B-cell non-Hodgkin lymphoma, with differential diagnoses of MZL or LPL.

Laboratory studies revealed an IgM kappa paraprotein level of 51 g/L, and bone marrow biopsy showed 30% infiltration by LPL. A positive MYD88 mutation supported a diagnosis of Waldenström's macroglobulinemia, a subtype of LPL characterized by bone marrow involvement and elevated IgM.

The patient began treatment in 2015 with six cycles of BR, achieving a partial response. His IgM level dropped to 3 g/L, and imaging showed near-complete resolution of lymphadenopathy. He declined a follow-up bone marrow biopsy. Two and a half years later, he relapsed with rising IgM (around 20 g/L) and anemia. Initiated 420 mg daily on ibrutinib, he developed musculoskeletal side effects, including myalgias and arthralgias, prompting a switch to Zanubrutinib.



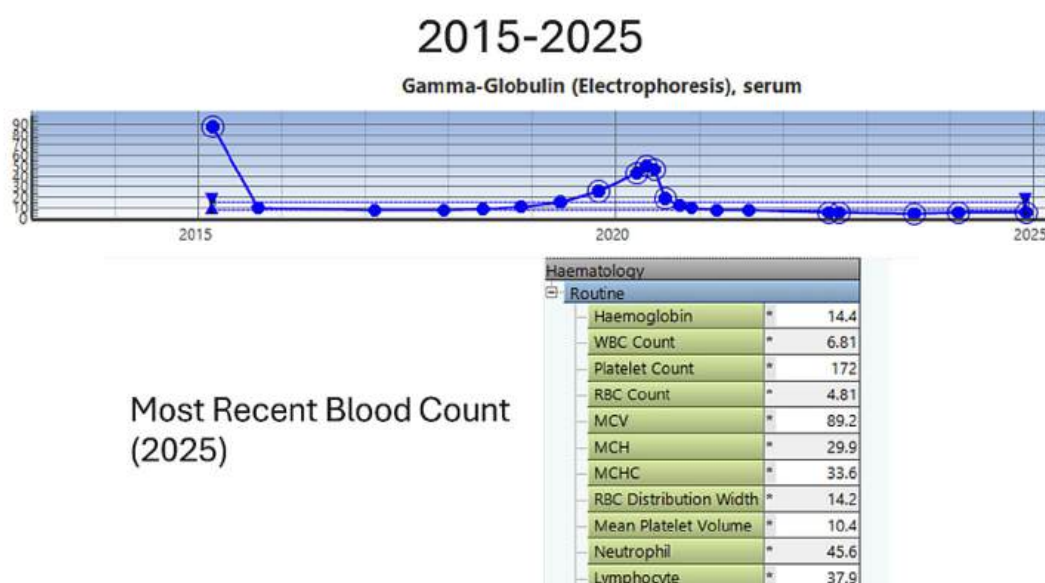
**Figure 4:** Comutation plot (left) for variants clustered according to best clinical response and MYD88 predictors curve (right) in response to Zanubrutinib<sup>8</sup>.

The new regimen was better tolerated, leading to symptom resolution, normalized hemoglobin, and undetectable M-protein, which are consistent with a very good partial response (**Figure 5**). This case demonstrates the clinical benefits of Zanubrutinib in elderly patients with LPL or Waldenström's macroglobulinemia, offering an effective and tolerable alternative for those with relapsed disease and intolerance to first-generation BTK inhibitors.

### **Zanubrutinib Redefines the Therapeutic Standard in R/R MZL**

The MAGNOLIA study underscores the significant advancement of Zanubrutinib in the treatment of R/R MZL. Its consistently high response rates across all

subtypes, paired with durable disease control and an encouraging safety profile, mark it as a reliable alternative to conventional therapies, particularly for patients who are elderly or medically fragile. The real-world case of an older patient who transitioned successfully from ibrutinib due to intolerance further illustrates the clinical relevance of Zanubrutinib in practice. With durable remissions, tolerability, and efficacy not dependent on MYD88 mutation status, Zanubrutinib fills a longstanding gap in the therapeutic landscape of indolent B-cell lymphomas. As treatment paradigms shift toward targeted agents, Zanubrutinib stands out as a compelling option that combines precision, potency, and safety, ultimately delivering sustained benefit where few alternatives exist.



**Figure 5:** Gamma-globulin (electrophoresis) serum graph (2015 -2025; top) and blood cell count (bottom) of case-study patient.



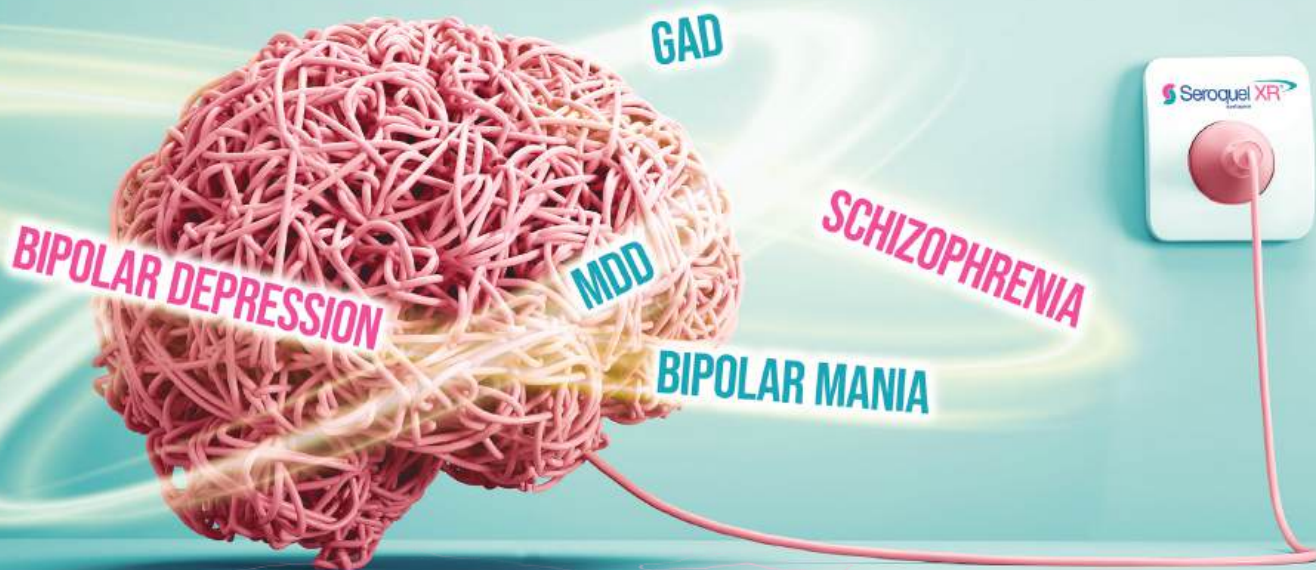
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- Generalised Anxiety Disorder (GAD) - 50-150mg/day\*

\* Dose range for acute treatment

**Abbreviated Prescribing Information:** Presentation: Quetiapine fumarate extended-release tablet. Indications: Bipolar Disorder: Maintenance treatment of bipolar I disorder; as monotherapy or in combination with lithium or sodium valproate, for 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 (MDD): Treatment of recurrent MDD in patients who are intolerant of, or who have an inadequate response to alternative therapies. Generalised Anxiety Disorder (GAD): Treatment of GAD. Dosage: Once daily, without food. Bipolar Disorder: Maintenance treatment: Use same dose as active treatment for prevention of manic, depressive or mixed episodes in bipolar disorder. Range 300-800 mg/day. Bipolar Depression: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4). Can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8. Acute Mania: 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. Schizophrenia: 300 mg (Day 1), 600 mg (Day 2) and up to 800 mg after Day 2. Range 400-800 mg/day depending on response and tolerability. Same dosage for maintenance therapy. Recurrent MDD: Once daily in the evening, 50 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 for maintenance therapy. GAD: 50 mg (Day 1 & 2), 150 mg (Day 3 & 4). Range 50-150 mg/day. Switching from Seroquel immediately release: Switch at equivalent total daily dose. Individual adjustments may be necessary. Elderly: 50 mg/day, increased in increments of 50 mg/day up to an effective dose depending on response and tolerability. Stower dose titration is recommended. Elderly MDD: 50 mg (Day 1-3), 100 mg (Day 4), 150 mg (Day 8), up to 300 mg depending on response and tolerability. Elderly GAD: 50 mg (Day 1-3), 100 mg (Day 4), 150 mg on Day 8. Patients with renal impairment: No dosage adjustment needed. Patients with hepatic impairment: 50 mg/day up to an effective dose. Contraindications: Hypersensitive to any components of this product. Precautions: Elderly patients with dementia-related psychosis or behavioural disorders; rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption; concomitant use with ADHD medication; conditions predisposing to hypotension; family history of QT prolongation, congenital long QT syndrome, heart failure, hypokalaemia or hypomagnesaemia, concomitant medicines known to prolong QTc interval; history of seizures, conditions that potentially lower seizure threshold; elevation in core body temperature; risk for aspiration pneumonia. Interactions: Centrally acting drugs: thioridazine, lorazepam; levodopa and dopamine agonists. CYP3A4 inhibitors: azole antifungals; macrolide antibiotics; protease inhibitors; grapefruit juice. Hepatic enzyme inducers: carbamazepine; phenytoin. Undesirable effects: Sedation; somnolence; insomnia; dizziness; syncope; headache; increased appetite; weight gain; dysphagia; dry mouth; nausea & vomiting; constipation; dyspepsia; tachycardia; palpitations; orthostatic hypotension; rhinitis; dyspnoea; blurred vision; abnormal dreams & nightmares; asthenia; dysarthria; fatigue; myalgia; peripheral edema; irritability; pyrexia; lipid changes; worsening of metabolic factors; elevations in serum transaminases (ALT, AST), γ-GT & serum prolactin; increases eosinophils; decreases in total T4, free T4 & total T3, and increases in TSH; leucopenia and/or neutropenia; mild asthenia; withdrawal symptoms after abrupt cessation. Full local prescribing information is available upon request.

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# ASCO 2026: Unprecedented Seven-Year Results from CROWN Redefine ALK-Positive NSCLC Treatment

The treatment paradigm for anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) has evolved dramatically with the advent of next-generation tyrosine kinase inhibitors (TKIs). The phase III CROWN study established lorlatinib as a highly effective first-line therapy, delivering durable systemic and intracranial disease control. At the 2026 American Society of Clinical Oncology (ASCO) Annual Meeting, updated seven-year follow-up results revealed a median progression-free survival (mPFS) not yet reached and a seven-year progression-free survival (PFS) rate of 55%. Importantly, the study also demonstrated a seven-year intracranial progression-free survival (PFS) rate of 92%, highlighting sustained central nervous system (CNS) protection. The concept of the “ALK diamond mutation” reflects the favourable prognosis associated with ALK-rearranged NSCLC, symbolising the profound therapeutic benefit afforded by modern targeted agents. This article reviews the long-term CROWN data and discusses their implications for clinical practice.

## Introduction

ALK-positive NSCLC accounts for approximately 3–5% of lung cancers and is characterised by oncogenic rearrangements of the ALK gene.<sup>1</sup> Historically, advanced NSCLC carried a poor prognosis; however, targeted therapies have revolutionised outcomes in this molecular subset.<sup>2</sup>

Today, the identification of an ALK rearrangement is often considered a “diamond” in lung cancer diagnosis. Despite the seriousness of metastatic disease, patients with ALK-positive tumours benefit from highly effective, relatively low-toxicity therapies that can produce deep responses and long-term survival. This favourable biology, combined with therapeutic advances, has reshaped expectations for disease control.<sup>3</sup>

## Overview of the CROWN Study

The global phase III CROWN trial compared lorlatinib, a third-generation ALK TKI, with crizotinib in treatment-naïve patients with advanced ALK-positive NSCLC. Initial and subsequent analyses consistently demonstrated superior efficacy with lorlatinib, including improved progression-free survival and intracranial response rates.<sup>3</sup>

Lorlatinib was rationally designed to overcome limitations of earlier ALK inhibitors, particularly resistance mutations and inadequate CNS penetration.

Lorlatinib has a compact, macrocyclic structure to physically overcome the steric hindrance and conformational binding shifts caused by mutations (like G1202R) that defeat earlier inhibitors.<sup>4</sup> When used in the first-line settings, because the cancer has not been previously exposed to or “sculpted” by earlier, weaker targeted therapies, it rarely harbours the complex or compound on-target mutations (like the deadly G1202R solvent-front mutation).<sup>5</sup> Lorlatinib is highly potent and effectively shuts down the primary ALK driver so completely that the cancer’s primary escape route is no longer through altering the ALK target site itself.<sup>6</sup> Instead of secondary ALK mutations, resistance—when it eventually occurs—is often driven by off-target or “bypass” signalling pathways that allow the tumour to grow independently of ALK.<sup>7</sup>

Lorlatinib is also highly lipophilic, specifically engineered to cross the blood-brain barrier, achieving high concentrations in the brain. Unlike older-generation drugs that accidentally or poorly crossed into the brain, lorlatinib was meticulously optimised from the ground up for CNS penetration using structure-based drug design and physicochemical parameter tuning.<sup>4</sup>



## Seven-Year Efficacy Outcomes

### Progression-Free Survival

The seven-year follow-up presented at ASCO 2026 provides unprecedented insight into long-term outcomes. The median progression-free survival remains unreached after seven years, indicating sustained benefit in a majority of patients. This represents a landmark achievement in metastatic NSCLC. The seven-year PFS rate of 55% further underscores the durability of response, suggesting that more than half of patients treated with first-line lorlatinib remain progression-free at this extended time point (**Figure 1**). Surprisingly, if the patients are progression-free by the second year, they will have approximately a 79% chance that they may remain progression-free at the end of the seventh year.<sup>6,8</sup>

These findings support the concept that ALK-positive NSCLC can be managed as a chronic condition in many patients. Early initiation of a highly potent TKI such as lorlatinib appears critical to achieving maximal long-term benefit.<sup>8</sup>

### Central Nervous System Protection

CNS involvement is common in ALK-positive NSCLC and remains a major clinical challenge. Lorlatinib's ability to penetrate the blood-brain barrier has translated into exceptional intracranial disease control. The CROWN study reported a seven-year intracranial progression-free survival rate of 92%, reflecting durable and sustained protection against CNS progression.<sup>8</sup>

This high level of intracranial control reduces the need for local CNS therapies, such as radiation or surgery, which are associated with potential neurocognitive

side effects. As a result, patients can maintain better neurological function and overall quality of life over time.<sup>8</sup>

## The Concept of the ALK “Diamond Mutation”

### A Symbol of Therapeutic Opportunity

The term “ALK diamond mutation” is used metaphorically to describe the uniquely favourable clinical outlook associated with ALK rearrangements. While advanced NSCLC is typically a severe diagnosis, the presence of an ALK alteration represents a “diamond” because.<sup>9,10</sup>

- Targeted therapies yield exceptionally high response rates
- Patients often experience prolonged survival
- Treatments are generally well tolerated compared with traditional chemotherapy

### Transforming Prognosis

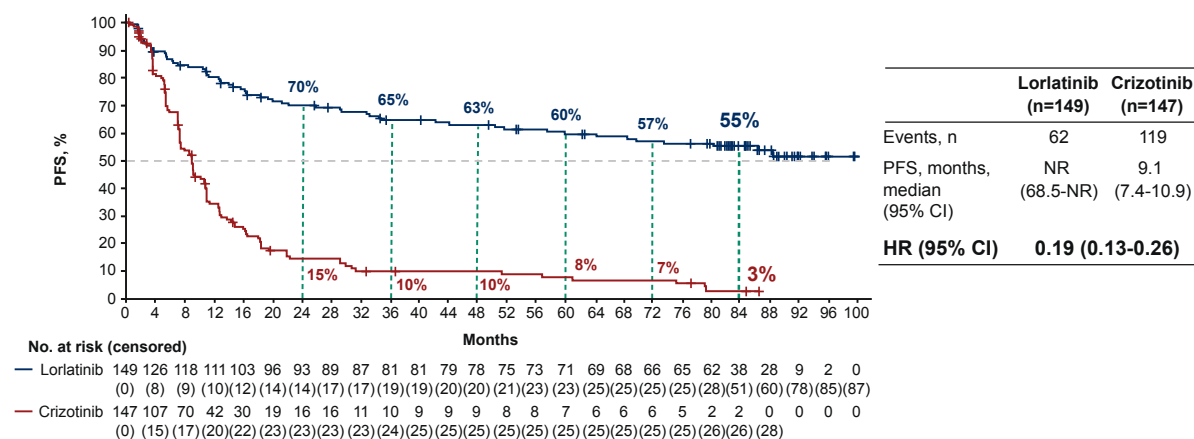
The availability of potent TKIs like lorlatinib and alectinib has fundamentally altered the natural history of this disease. Patients with ALK-positive NSCLC now frequently achieve long-term disease control, redefining expectations for metastatic cancer.<sup>8,10</sup>

### Importance of Early Detection

This concept highlights the critical role of comprehensive molecular testing.<sup>11</sup> Identifying ALK rearrangements at diagnosis enables timely initiation of optimal therapy, significantly improving outcomes.<sup>12</sup>

## Comparative Context

Compared with earlier generations of ALK inhibitors, third-generation agents demonstrate clear advantages:



**Figure 1:** PFS by investigator assessment in intention-to-treat population<sup>6</sup>. CI: confidence interval; HR: hazard ratio; NR: not reached; PFS: progression free survival

- Crizotinib (first-generation): Limited durability and poor CNS penetration<sup>13</sup>
- Second-generation inhibitors: Improved outcomes but eventual resistance<sup>14</sup>
- Third-generation inhibitors: Superior long-term PFS and exceptional intracranial efficacy. The seven-year data from CROWN firmly establish lorlatinib as a leading first-line standard of care<sup>6,8</sup>

### Safety and Tolerability

The safety profile of lorlatinib was similar to that reported in the primary analysis of CROWN and in subsequent follow-up analyses, with no new safety signals detected-suggesting no cumulative toxicity-with additional follow-up.<sup>6,15</sup> Lorlatinib has a manageable safety profile, though it requires careful monitoring. Common adverse events include hyperlipidaemia, cognitive and mood effects, and peripheral oedema. These side effects are generally manageable with dose adjustments and supportive care, allowing most patients to continue long-term therapy.<sup>6</sup>

### Implications for Clinical Practice

The updated findings from the CROWN study have several key implications:

- **Frontline ALK Inhibitors:** Early use maximizes both systemic and intracranial control

- **CNS-First Strategy:** Preventing intracranial progression is essential in optimising long-term outcomes
- **Routine Molecular Testing:** Detecting ALK alterations is critical to unlocking effective targeted therapy
- **Chronic Disease Management:** Long-term therapy requires ongoing monitoring and multidisciplinary care

### Conclusion

The seven-year follow-up of the CROWN study represents a milestone in the treatment of ALK-positive NSCLC. With a median PFS not yet reached and a seven-year PFS rate of 55%, lorlatinib provides unprecedented durability of disease control. Its remarkable 92% seven-year intracranial progression-free survival rate highlights its ability to protect against CNS progression, a key determinant of patient outcomes.

The concept of the ALK “diamond mutation” encapsulates the optimism now associated with this disease subtype. Although metastatic NSCLC remains serious, patients with ALK rearrangements benefit from highly effective targeted therapies that enable prolonged survival and preserved quality of life.

These findings reinforce lorlatinib’s role as a transformative therapy and set a new benchmark for long-term outcomes in precision oncology.



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Reference: 1. Lam RW, et al. Can J Psychiatry. 2024;69(9):641-687. 2. REXULTI® Hong Kong Prescribing  
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# Coffee or Tea? Caffeine Consumption— a New Perspective of Dementia Prevention

Dementia is a growing global health concern, with rising prevalence driven by population ageing and limited curative treatment options. Consequently, preventive strategies have become a central focus of research. Among modifiable lifestyle factors, caffeine consumption—particularly through widely consumed beverages such as coffee and tea—has attracted increasing attention for its potential neuroprotective effects. This article reviews current evidence on the association between caffeinated coffee and tea intake and the risk of dementia, highlighting epidemiological findings that suggest a non-linear, dose-dependent relationship, in which moderate consumption is linked to the greatest risk reduction. Proposed biological mechanisms include adenosine receptor antagonism, inhibition of amyloid precursor protein processing, and antioxidant and anti-inflammatory effects. Differences between coffee and tea are also explored, with tea containing additional bioactive compounds such as epigallocatechin gallate and L-theanine that may enhance cognitive benefits. Despite promising findings, the underlying mechanisms remain incompletely understood, and direct comparisons between coffee and tea are limited. Overall, these findings underscore the importance of moderate caffeine intake within a broader framework of lifestyle-based dementia prevention.

## Introduction

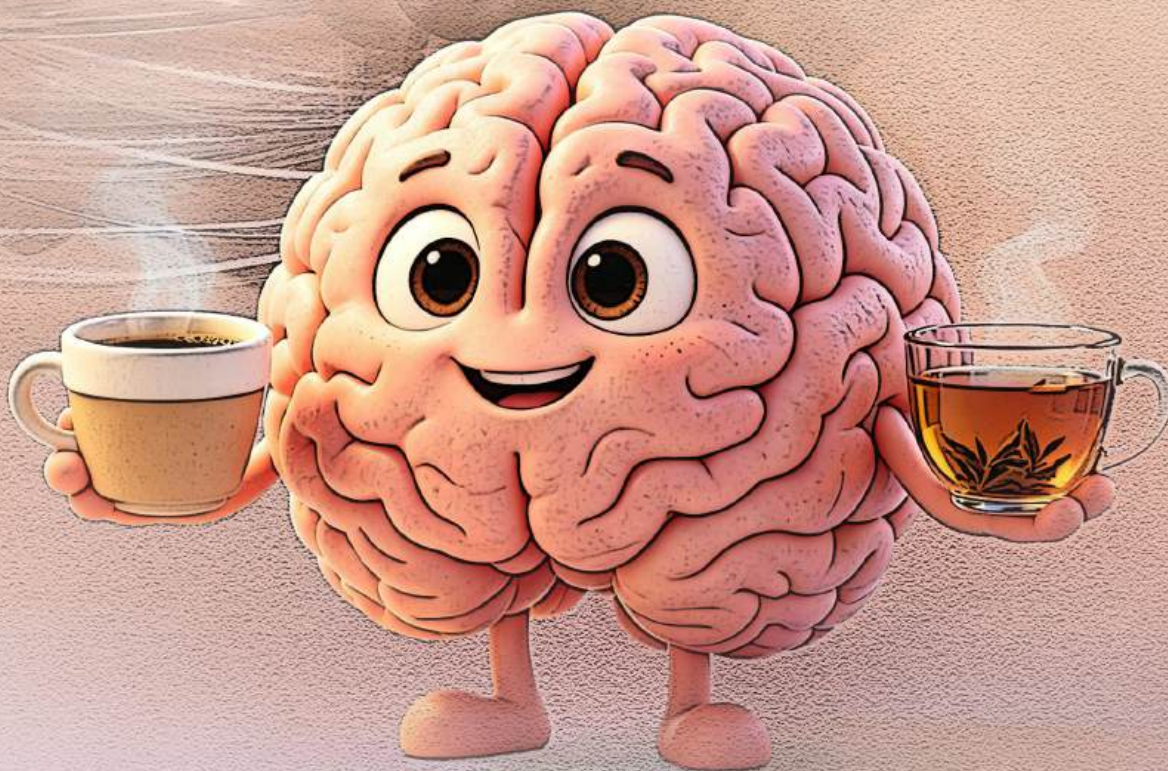
Dementia is a chronic syndrome that causes cognitive decline in affected patients, usually in the elderly.<sup>1,2</sup> It is estimated that dementia affects up to 57 million people worldwide and is projected to reach 152.8 million cases by 2050, because of population ageing, making it a prominent global public health concern.<sup>3,4</sup> The treatments currently available mainly focus on management of symptoms, and are unable to cure the underlying diseases.<sup>5,6</sup> Indeed, prevention remains the utmost focus of dementia research.<sup>7</sup> While certain risk factors such as genetics and age cannot be changed, lifestyle choices—including blood pressure management, regular physical activity, smoking cessation, moderate alcohol consumption, and a healthy diet—can be modified to help preserve cognitive function.<sup>3,8</sup> It is well known that common caffeinated beverages such as coffee and tea possess potential cognitive benefits, especially in sleep-deprived

individuals.<sup>9</sup> Recent studies have even pointed out that moderate caffeine consumption may be associated with lower risk of dementia.<sup>10,11</sup>

## What are Dementia and Cognitive Decline?

As aforementioned, dementia is an umbrella term for a syndrome—not a specific disease—characterised by a chronic, progressive decline in cognitive function severe enough to interfere with daily life. It is caused by various underlying neurodegenerative conditions and brain injuries, with over 100 identified types and causes.<sup>2,3</sup> The most common types of dementia include Alzheimer's disease (AD), vascular dementia, and Lewy body dementia.<sup>12</sup> Rarer dementia types also include frontotemporal dementia, young-onset dementia, or when multiple dementia types are present, mixed dementia.<sup>13</sup>

Dementia symptoms present differently across patients and are shaped by the stage and progression of the



disease. Early-stage dementia (Stages 1–3) is typically characterized by memory impairment and deficits in reasoning, communication, planning, and organizational skills.<sup>2,3,14</sup> In middle-stage dementia (Stages 4–5), the patient's mood, behaviour, and even personality (more common in the case of frontotemporal dementia) may change, leading to struggle with daily tasks and loss of independence.<sup>2,3,14,15</sup> In the final stage of dementia (Stages 6–7), patients may experience severe cognitive decline, and exacerbation of the aforementioned symptoms.<sup>14</sup> Ultimately, dementia alters nearly every aspect of daily living, profoundly impacting both patients and their caregivers.

In addition to its many debilitating symptoms, dementia also induce emotional distress in patients. Emotional distress in dementia is often a signal of an unmet need or physical discomfort, rather than just a symptom of the disease. It can manifest as agitation, crying, wandering, or aggression.<sup>16</sup> Insecurity, anxiety, and social stigma collectively exacerbate the psychological decline experienced by individuals with dementia.<sup>15,17</sup>

Such distress can extend to caregivers, manifesting in deteriorating physical health and psychological resilience.<sup>18,19</sup> It is important to note that dementia also imposes a significant burden on healthcare systems. According to an estimate, direct health care spending attributable to Alzheimer's disease and related dementias (ADRD) will reach \$1.6 trillion in 2050, or 9.4% of projected health spending worldwide.<sup>20,21</sup>

Early intervention and prevention of dementia are thought to be beneficial. Barnett et al. demonstrated in their symptomatic treatment model that a maximum net benefit would be produced 8 years prior to a standard diagnosis, with efficacy decreasing by 17% for every year that interventions were delayed.<sup>22</sup> The results were even more pronounced in their disease-modifying model, the maximum net benefit being 15 times larger than that of the symptomatic treatment.<sup>22</sup> Their findings are consistent with previous research, indicating the necessity of early interventions by means of cognitive training, and lifestyle changes such as physical activity, psychosocial support, and dieting.<sup>23,24</sup>

## Association between Caffeine and Dementia

Research has shown that caffeine consumption is associated with a lower risk of dementia. Zhang et al. performed a prospective cohort study on participants without cancer, Parkinson disease, or dementia at the time of entry to elucidate the association between caffeine consumption, cognitive functioning, and dementia.<sup>11</sup> After adjusting for potential confounders, there were 330 cases per 100,000 persons-years in the lowest consumption quartile of caffeinated coffee, while there were 141 cases per 100,000 persons-years in the highest consumption quartile, resulting in a hazard ratio of 0.82 (95% CI, 0.76-0.89).<sup>11</sup> A similar effect is observed in tea consumption: 321 per 100,000 person-years for the tertile of lowest tea intake and 201 per 100,000 person-years for the tertile of highest tea intake.<sup>11</sup> Both results, supported by other reviews and analyses, suggest a protective effect of caffeine against dementia.<sup>10,11,25,26</sup>

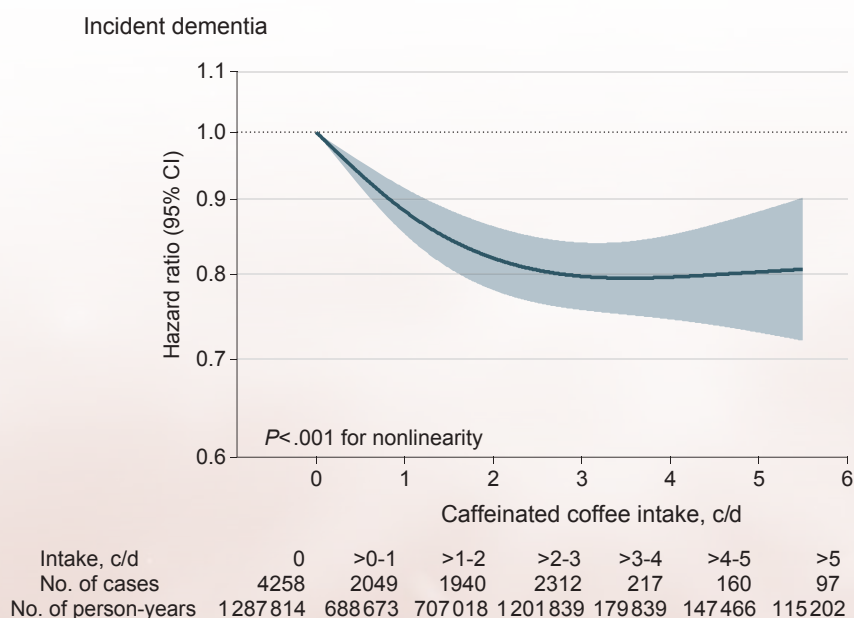
Across multiple studies, the relationship between caffeine consumption and dementia is considered non-linear. Zhang et al. demonstrated through dose-response analyses that caffeine consumption was inversely associated with dementia risk in a non-linear manner (**Figure 1**).<sup>11</sup> This finding is consistent with other meta-analyses and reviews, commonly suggesting a J-shaped or U-shaped dose-response graph.<sup>10,25,26</sup> Thus, it is suggested that moderate consumption of caffeinated coffee has the most effective

neuroprotective effect against dementia.<sup>10,11, 25,26</sup> This observation prompts important questions regarding the biological mechanisms that may drive such a unique dose-response relationship.

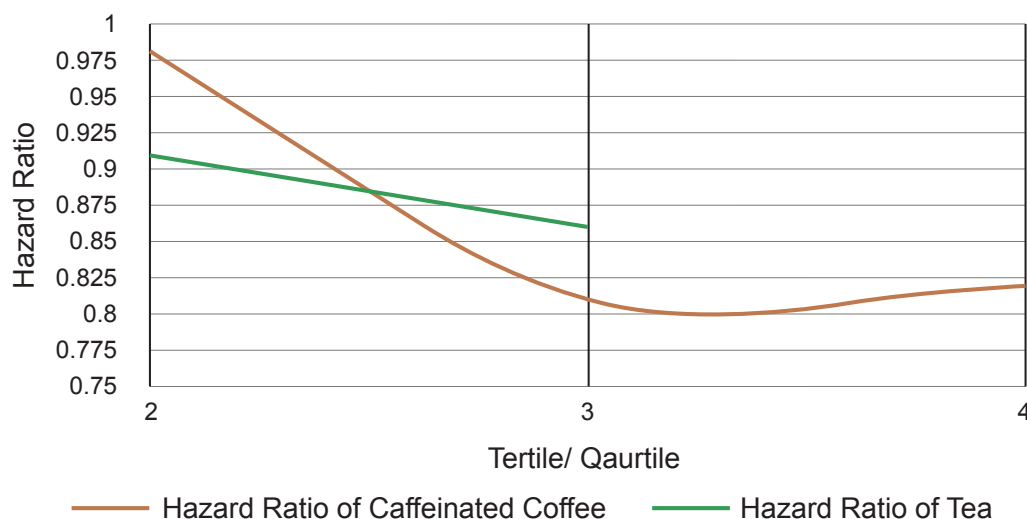
## Proposed Mechanism of Action for Neuroprotection

A prominent mechanism proposed is the antagonistic nature of caffeine against adenosine receptors. The blocking of both A<sub>1</sub> and A<sub>2A</sub> receptors have been shown to impede the pathological changes induced by amyloid  $\beta_{25-35}$  (A $\beta_{25-35}$ ), a highly toxic, 11-amino-acid fragment of the full-length A $\beta$  protein.<sup>7</sup> Thus, caffeine may exert its neuroprotective effects via decreasing protein misfolding and A $\beta$  plaque formation.<sup>27</sup>

Another hypothesised mechanism for caffeine's neuroprotective property is its inhibition of amyloid precursor protein (APP) processing. Caffeine is said to suppress  $\beta$ - and  $\gamma$ -secretase activity.<sup>11</sup>  $\beta$ -secretase is responsible for the proteolytic cleavage and subsequent generation of membrane-tethered C-terminal fragments (CTF) from APP.<sup>7</sup> Caffeine stimulates protein kinase A (PKA) activity and reduces nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), resulting in the inactivation of  $\beta$ -secretase.<sup>28</sup> CTFs are often directly subjected to a second cleavage by the  $\gamma$ -secretase complex, producing multiple A $\beta$  isoforms, namely the highly neurotoxic A $\beta_{1-42}$ .<sup>7</sup> Caffeine reduces glycogen synthase kinase-3 alpha (GSK-3 $\alpha$ ) levels, thereby diminishing  $\gamma$ -secretase activity.<sup>28</sup>



**Figure 1:** Association between Dementia and Caffeinated Coffee Intake.<sup>11</sup> c/d: cups per day; CI: confidence interval



**Figure 2:** Neuroprotective Effects of Caffeinated Coffee and Tea.<sup>11</sup>

Antioxidant and anti-neuroinflammatory properties of caffeine may also contribute to its neuroprotective effects. Neuronal oxidative stress is a primary driver of neuronal damage in both AD and vascular dementia.<sup>29</sup> Caffeine can act as an antioxidant by inactivating NF- $\kappa$ B and decreasing reactive oxygen species generation.<sup>7,30</sup> By directly suppressing the nuclear translocation of NF- $\kappa$ B and its subsequent transcriptional events, caffeine also helps reduce neuroinflammation.<sup>7</sup> Decreased NF- $\kappa$ B production reduces downstream production of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumour necrosis factor-alpha (TNF- $\alpha$ ), protecting oligodendrocytes and astrocytes from inflammatory damage.<sup>31</sup>

The elevated risk of dementia associated with high caffeine intake is likely multifactorial. Recall the non-linearity of the dose-response curve of caffeine against dementia risk—evidence suggests that the neuroprotective effects of caffeine may diminish at higher levels of consumption.<sup>11</sup> A plausible explanation includes a physiological threshold for caffeine absorption, disruption of sleep quality, and exacerbation of anxiety.<sup>11</sup> These adverse effects may counteract the potential cognitive benefits of caffeine.

### ☕ Differences between Caffeinated Coffee and Tea in Neuroprotection

Despite the lack of randomised clinical trials comparing the neuroprotective properties of caffeinated coffee and tea, much research has shown consistent association between tea consumption and cognitive function.<sup>32</sup> The presence of epigallocatechin-3-gallate (EGCG)

and L-theanine in tea may increase the neuroprotective capacity of tea consumption.<sup>11</sup> EGCG has been proven to improve cognitive functioning in cognitive-deficit diseases such as AD, albeit without a clear explanation of its mechanism of action.<sup>33</sup> Similarly, L-theanine improves cognitive functions—better performance is observed in the L-theanine group than control in terms of attention and working memory tasks.<sup>34</sup> Therefore, it would seem that the bioactive compounds present in tea may promote more consistent improvements in cognitive function compared to those associated with caffeinated coffee consumption.

On the other hand, caffeinated coffee consumption may be likely to have more pronounced effect in neuroprotection. Zhang et al. computed the hazard ratios of each tertile/quartile of caffeinated coffee and tea consumption against the lowest consumption group (the first tertile/quartile). It appeared that except for the second lowest intake tertile/quartile, the caffeinated coffee group showed lower hazard ratios (**Figure 2**).<sup>11</sup>

However, due to the lack of head-to-head studies comparing the neuroprotective effects of caffeinated coffee and tea, there is no conclusive answer as to which offers greater benefits,

### ☕ So... Coffee or Tea?

Although current evidence suggests that caffeinated coffee and tea may be associated with a reduced risk of dementia, the underlying mechanisms remain incompletely understood and require further investigation. For individuals concerned about

dementia prevention, it is important to recognise that any potential neuroprotective benefit appears to be linked to moderate consumption rather than excessive intake. Ultimately, the question should perhaps not be framed as simply “coffee or tea”, but rather considered within the context of a broader lifestyle approach—one that includes a balanced diet, regular physical activity, cognitive engagement, adequate sleep, good mental well-being, avoidance of excessive alcohol consumption, and consultation with a healthcare professional when appropriate.<sup>22,23</sup>

## Conclusion

Current evidence suggests that caffeinated coffee and tea may contribute to a reduced risk of dementia, particularly when consumed in moderation. However, the relationship is complex and appears to follow a non-linear pattern, with excessive intake potentially diminishing the benefits. While several plausible biological mechanisms have been proposed, including modulation of amyloid pathways and neuroinflammation, definitive causal pathways remain to be fully established. Furthermore, although both coffee and tea demonstrate potential neuroprotective properties, insufficient comparative evidence prevents a clear conclusion regarding their relative effectiveness.

Importantly, caffeine consumption should not be viewed in isolation. The prevention of dementia is best approached through a comprehensive lifestyle strategy that integrates a balanced diet, regular physical activity, cognitive engagement, adequate sleep, and good mental health, alongside avoidance of excessive alcohol intake and appropriate medical consultation. Future research, particularly well-designed clinical and mechanistic studies, is needed to clarify the role of caffeine and its interaction with other lifestyle factors in dementia prevention.



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# THE FIRST AND ONLY BTKi APPROVED IN FOLLICULAR LYMPHOMA

**BRUKINSA® + Obinutuzumab reduced the relative risk of progression or death by 50% vs obinutuzumab alone<sup>1</sup>**

**Approx. 70% of patients had sustained responses at 18 months with BRUKINSA® + Obinutuzumab<sup>1</sup>**

## Reference

1. Zinzani PL, Mayer J, Flowers CR, et al. ROSEWOOD: A Phase II Randomized Study of Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab Monotherapy in Patients With Relapsed or Refractory Follicular Lymphoma. J Clin Oncol. 2023; 41(33):5107-5117

## Abbreviated Prescribing Information

**Presentation:** BRUKINSA® (zanubrutinib) capsules 80mg. **Indication:** BRUKINSA® as monotherapy is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. BRUKINSA® as monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy. BRUKINSA® as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL). BRUKINSA® in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies. **Dosage & Administration:** The recommended total daily dose of BRUKINSA® is 320 mg. The daily dose may be taken either once daily (four 80 mg capsules) or divided into two doses of 160 mg twice daily (two 80 mg capsules). **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special Warnings & Precautions:** (1) Haemorrhage: Warfarin or other vitamin K antagonists should not be administered concomitantly with BRUKINSA®. Patients should be monitored for signs and symptoms of bleeding and monitor complete blood counts. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with BRUKINSA®, (2) Infections: Consultation with a liver disease expert physician is recommended for patients who test positive for HBV or have positive hepatitis B serology, before initiating treatment. Patients should be monitored and managed according to the medical standards to prevent hepatitis B reactivation. Consider prophylaxis according to standard of care in patients who are at increased risk for infections. Patients should be monitored for signs and symptoms of infection and treat appropriately, (3) Cytopenia: Monitor complete blood counts monthly during treatment, (4) Second primary malignancies including skin cancer: Advise patients to use sun protection, (5) Atrial fibrillation and flutter: Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate, (6) Women of childbearing potential: Women of childbearing potential must use a highly effective method of contraception while taking BRUKINSA®, (7) BRUKINSA® contains sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. **Undesirable effects:** The most commonly occurring adverse reactions (≥20%) were neutropenia, thrombocytopenia, upper respiratory tract infection, haemorrhage/haematoma, rash, bruising, anaemia, musculoskeletal pain, diarrhoea, pneumonia and cough. Refer to the full prescribing information for other undesirable effects. **Interactions:** If a strong and moderate CYP3A inhibitor must be used, reduce the BRUKINSA® dose for the duration of the inhibitor use. Concomitant use with strong and moderate CYP3A inducers should be avoided. No clinically significant differences in BRUKINSA® pharmacokinetics were observed when co-administered with gastric acid reducing agents. **Pregnancy & Lactation:** BRUKINSA® should not be used during pregnancy. Breast-feeding should be discontinued during treatment with BRUKINSA®. **Full prescribing information should be consulted prior to prescribing.**



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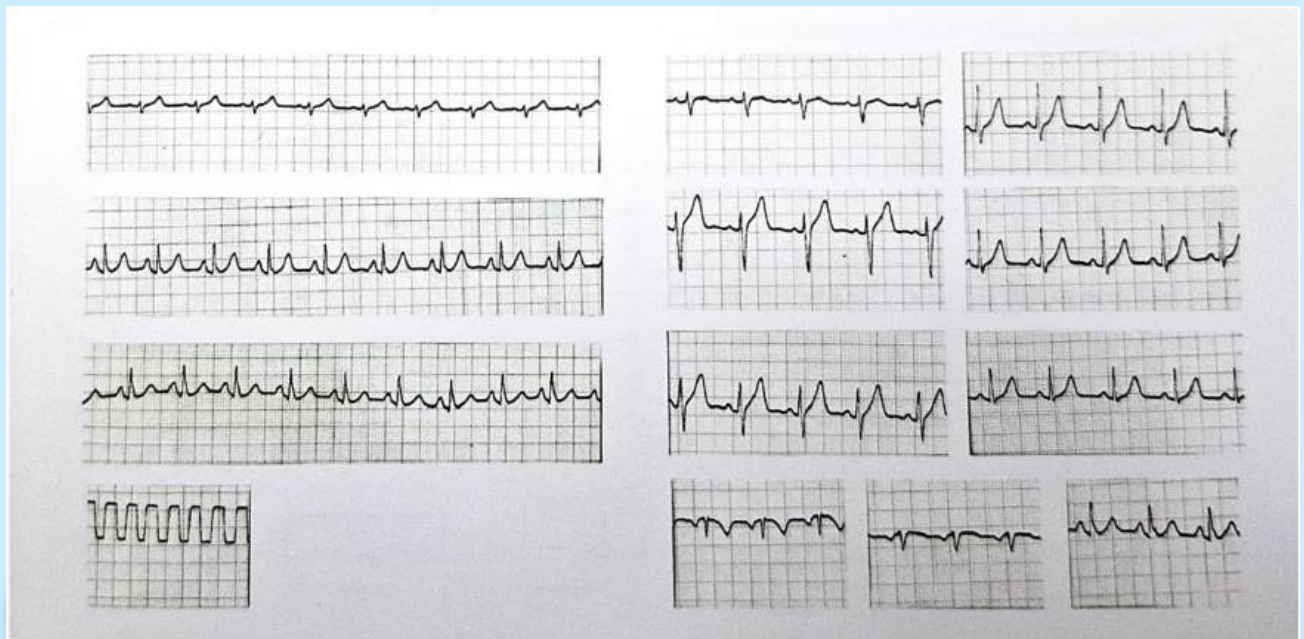


## ECG CME JUNE 2026 (0.5 CME POINTS)

Dr. Pun Chiu On, Specialist in Cardiology

### History:

This 56 year old man is a construction site worker. He was also a chronic smoker for many years. He came to see you because of productive cough with yellow septum. He also complained of shortness of breath. Examination of chest showed bronchial wheezing.



**Question:** What is the ECG diagnosis?

(Please tick one)

- ☐ Normal ECG
- ☐ Right atrial enlargement
- ☐ Left atrial enlargement
- ☐ Right ventricular hypertrophy
- ☐ Left ventricular hypertrophy

Please complete the Self-Study by visiting our website: <https://cmevideo.hkdu.org/> or scan the QR code to submit your answers on or before **15-JULY-2026**



SCAN ME

## Answer to April 2026 Issue's CME

### ECG diagnosis:

Generalised low voltage.

### Reason for the ECG diagnosis:

- The minimum voltage of R wave in chest lead is at least one R wave > 8 mm. All the R waves in the chest leads in this ECG are less than 8 mm.

### Possible aetiology:

- Obesity
- Emphysema
- Pericardial effusion
- Hypothyroidism
- Pneumothorax

### Significance:

It depends on the underlying aetiology.

### Principle of management:

Manage the underlying cause.

### Management of this patient:

This patient was obese. Her BMI was  $29.5 \text{ kg/m}^2$ . Her thyroid function was normal. She was advised on weight reduction.

# Upcoming Academic Events

in Hong Kong



June – September 2026

Asia Pacific Alliance for the  
Control of Influenza

## APACI Respiratory Diseases Conference 2026

**Jun 25**

Thursday



The Hong Kong College of  
Family Physicians

## Hong Kong Primary Care Conference 2026

**Jun 26-28**

Friday-Sunday



Institute of Digestive Disease,  
The Chinese University of Hong Kong

## International Digestive Disease Forum

**Jun 27-28**

Saturday-Sunday



The Hong Kong Polytechnic University's  
College of Professional and Continuing  
Education

## Reviewing Universal Healthcare Coverage in the Asia-Pacific

**Jul 31**



Hong Kong Dental Association

## The 15<sup>th</sup> Hong Kong International Dental Expo And Symposium

**Aug 21-23**



Union for International Cancer  
Control

## The World Cancer Congress 2026

**Sep 24-26**



## THERAPEUTIC INDICATIONS<sup>1</sup>

- ✕ Treatment of osteoporosis in postmenopausal women at increased risk of fracture
- ✕ Treatment of osteoporosis in men at increased risk of fracture
- ✕ Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture

## BONE STRENGTH

=

**BONE  
QUALITY**

+

**BONE  
MINERAL  
DENSITY**

The current concept of **"BONE QUALITY"** Bone quality, which has been defined as **"The sum of all characteristics of bone that influence the bone's resistance to fracture"**, is completely independent of bone mineral density.<sup>2</sup>



### Microcomputer tomography images of iliac crest in a postmenopausal woman treated with teriparatide<sup>3</sup>

Teriparatide treatment of postmenopausal women with osteoporosis significantly increased cancellous bone volume and connectivity, improved trabecular morphology, and increased cortical bone thickness.

**TERIPARATIDE INCREASES CANCELLOUS BONE VOLUME, IMPROVES BONE ARCHITECTURE, AND INCREASES CORTICAL THICKNESS.<sup>3</sup>**



FORTEO® Abbreviated Prescribing Information  
For healthcare professionals use only  
Full prescribing information is available upon request

#### References

1. Forteo Hong Kong Prescribing Information.
2. Kuroshima S, et al. J Prosthodont Res. 2017; 61: 353–362.
3. Jiang Y, et al. J Bone Miner Res. 2003;18(11):1932-1941.

# Oral Semaglutide in Patients with Type 2 Diabetic (T2D): Reducing Risk of Heart Failure (HF)

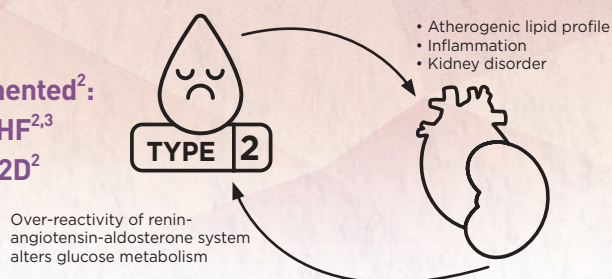
by Andrew Chan

## Introduction

Up to **57%** of T2D patients have HF<sup>1</sup>

**The interplay** between HF and T2D is well-documented<sup>2</sup>:

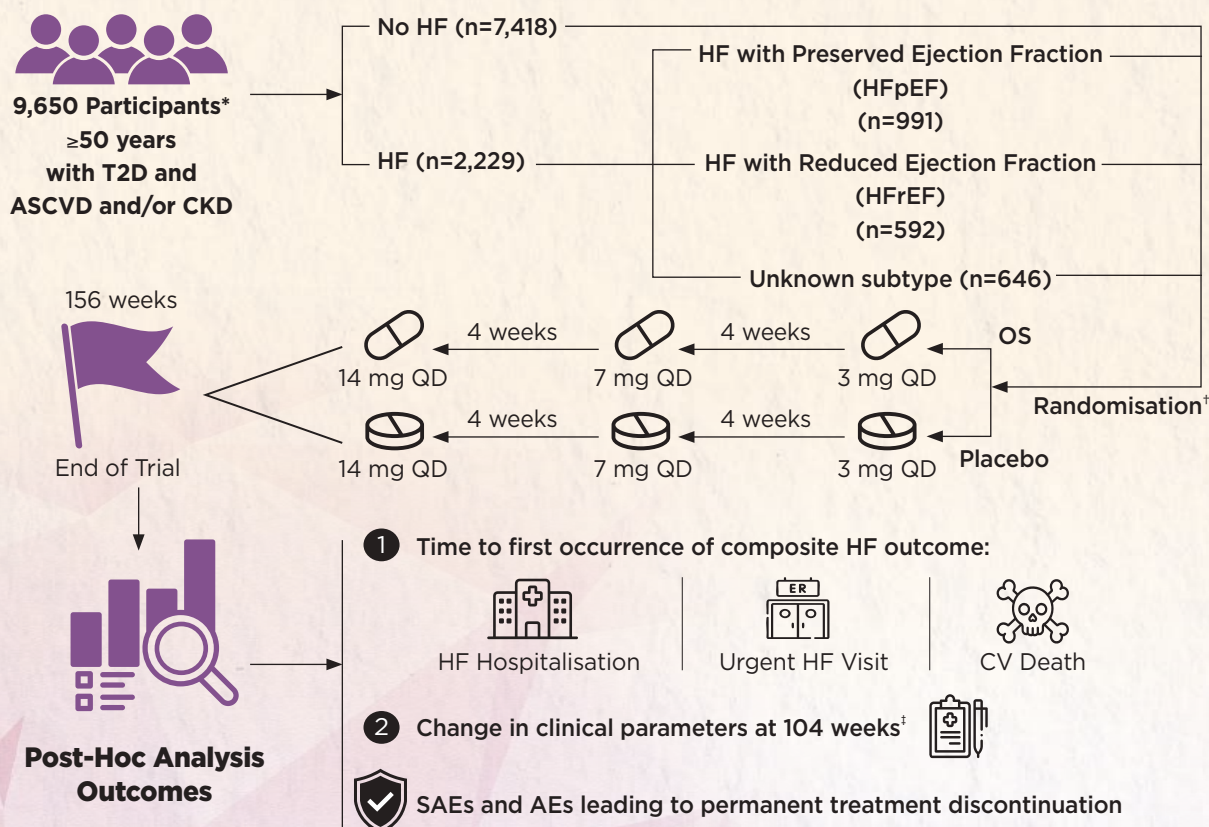
- T2D patients → increased risk of new onset of HF<sup>2,3</sup>
- HF patients → increased risk of new onset of T2D<sup>2</sup>
- HF in T2D → increased risk of hospitalisation and mortality<sup>1,4</sup>



**Oral semaglutide (OS) is the first FDA-approved oral glucagon-like peptide 1 (GLP-1) receptor agonist and presents a new opportunity for T2D management<sup>5</sup>**

## SOUL: Secondary Analysis Study Design<sup>1,6</sup>

**Double-blind | Randomised | Placebo-controlled  
444 Centres in 33 Countries**



\*Individuals with HF in NYHA class IV were not eligible for inclusion

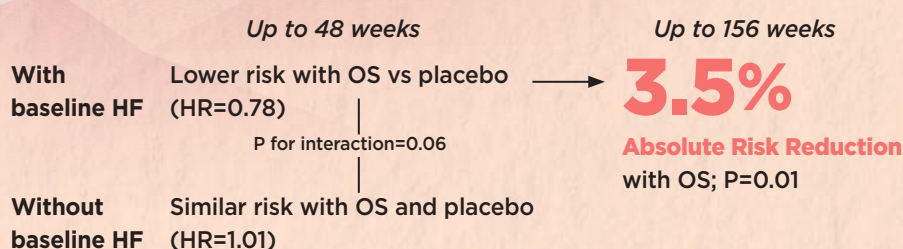
<sup>†</sup>Randomised in a 1:1 ratio to receive once-daily OS or matching placebo

<sup>‡</sup>HbA1c, body weight, high-sensitivity C-reactive protein, and systolic/diastolic blood pressure



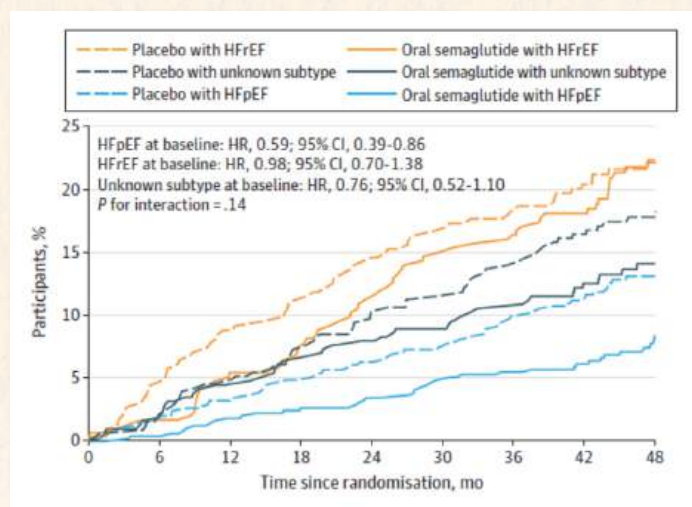
## Results<sup>1</sup>

### 1 HF composite outcome by HF at baseline



### HF composite outcome by HF subtype in patients with HF at baseline

OS vs. Placebo; Up to 48 Weeks



**HR=0.98**

(95% CI, 0.70-1.38)



HFrEF

**HR=0.76**

(95% CI, 0.52-1.10)



Unknown

**HR=0.59**

(95% CI, 0.39-0.86)



HFpEF

### 2 No evidence of heterogeneity in the treatment effect of OS based on HF status at baseline across efficacy clinical parameters



- **No difference in occurrence** of  $\geq 1$  SAE between OS and placebo
- **Fewer patients experienced  $\geq 1$  SAE with OS than placebo (46.0% vs. 52.5%) in HFpEF subgroup**



## Key Takeaway<sup>1</sup>

The SOUL data support the potential benefit of oral semaglutide in reducing HF events in people with T2D and HF

**Abbreviations:** AE, adverse event; ASCVD, atherosclerotic cardiovascular diseases; CI, confidence interval; CKD, chronic kidney diseases; CV, cardiovascular; FDA, Food and Drug Administration; GLP-1, glucagon-like peptide 1; HbA1c, glycated haemoglobin A1c; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; NYHA, New York Heart Association; OS, oral semaglutide; T2D, type 2 diabetes; QD, once daily; SAE, severe adverse event

**References:** 1. Pop-Busui, et al. JAMA Internal Medicine. 2026;186(4):426. 2. Palazzuoli A, and Iacoviello M. Heart Failure Reviews. 2022;28(3):585-96. 3. Pop-Busui R, et al. Diabetes Care. 2022;45(7):1670-90. 4. Panchal K, et al. Diabetes Research and Clinical Practice. 2024;207(111054). 5. Hughes S, et al. CLINICAL PHARMACOLOGY UPDATE. 2020;38(1):109-11. 6. McGuire DK, et al. New England Journal of Medicine. 2025;392(20):2001-12.

# On-the-Pulse

## Global Health

### World No Tobacco Day 2026<sup>1</sup>

World No Tobacco Day 2026, themed "Unmask the appeal - countering tobacco and nicotine addiction," targets the aggressive marketing and product design strategies industries use to addict younger generations. Globally, 40 million adolescents use tobacco, and 15 million use e-cigarettes, making youths nine times more likely to vape than adults. The Pan American Health Organization (PAHO) and WHO advocate for strict policy interventions, including banning flavours, implementing plain packaging, and prohibiting advertising. The campaign empowers communities by providing toolkits to build nicotine-free schools and comprehensive guides supporting individuals in breaking the cycle of nicotine addiction.

## Psychiatry

### Network Meta-Analysis on Non-Pharmacological Interventions for SUD<sup>2</sup>

A network meta-analysis of 117 randomised controlled trials across 25 countries evaluated the efficacy of non-pharmacological interventions on anxiety, depression, and quality of life (QoL) in 11,177 individuals with substance use disorders (SUDs). The study found that several interventions, including neuromodulation, mind-body therapy, and acupuncture, effectively reduced short-term anxiety and depressive symptoms compared to controls. SUCRA rankings identified neuromodulation as the top-ranked option for anxiety and QoL, while mind-body therapy performed best for depression. However, short-term benefits for QoL remained uncertain. Selection of interventions should integrate these rankings with feasibility, local capacity, and patient preferences.

## Paediatric Neurology

### Clinical Pharmacology and Reproductive Toxicology in Epilepsy Management<sup>3</sup>

A Danish cohort study of 1,180,308 singleton children investigated whether paternal valproate use during spermatogenesis increased neurodevelopmental disorder (NDD) risks in offspring. Prompted by a conflicting European Medicines Agency safety report, researchers compared 961 children exposed to paternal valproate monotherapy against 1,401 children exposed to lamotrigine or levetiracetam. The main analysis revealed no significant association with NDDs (adjusted hazard ratio, 1.02). This safety profile remained robust across various secondary and sensitivity adjustments. Ultimately, the findings suggest paternal antiseizure medication exposure during conception poses no major risk to offspring, though researchers emphasised a need for full study transparency.

 Neurology

## The Neurobiology of Circular RNA in Hippocampal Function<sup>4</sup>

A neuroscience study investigated how the brain-enriched circular RNA, *circHomer1*, regulates hippocampus-dependent learning and memory. By examining male mice, researchers found that *circHomer1* exhibits an experience- and activity-dependent expression pattern within the hippocampal CA1 subregion. Depleting *circHomer1* impaired dendritic spine morphology, reduced postsynaptic protein expression, and caused significant spatial learning and memory deficits across multiple behavioural tests, such as the Barnes maze. Mechanistically, *circHomer1* serves as a vital molecular bridge between the motor protein Kinesin 1 and neuronal ribonucleoprotein granules, facilitating the dendritic transport of synaptic mRNAs essential for structural plasticity.

 Antiviral Pharmacology

## The Pharmacology of Novel Carbobicyclic Nucleoside Analogues<sup>5</sup>

A medicinal chemistry study investigated a new class of nucleoside analogues built on a synthetically accessible carbobicyclic scaffold designed to conformally mimic ribose. The researchers found that library screening revealed pan-antiviral activity against several viruses, including HCV, HSV, and influenza. Specifically, the uracil analogue 2a inhibited influenza A virus replication by directly disrupting viral polymerase activity. Metabolism analysis suggested that the compounds did not require complex prodrug formulations; instead, they are readily phosphorylated into active triphosphates that bypass human polymerases, avoiding toxicity. The findings suggest this novel architecture provides a promising chemotype for safer pan-antiviral therapeutics.

 Nutritional Science

## Reproductive Cancers Narrow the Female Survival Advantage in Midlife<sup>6</sup>

A modelling study used a quantitative systems pharmacology framework to examine whether dietary patterns and drinking water quality impact gastric nitrosation, a known pathway for generating carcinogenic N-nitroso compounds (NOCs) from ingested nitrate and nitrite. The researchers found that individuals adhering to a standard Western diet paired with high-nitrate drinking water faced the greatest risk of gastric NOC formation. Conversely, shifting toward a Mediterranean diet or incorporating vitamin C supplementation significantly lowered gastric nitrite concentrations and NOC levels. The findings suggest that vitamin C may reduce cancer-linked digestive chemical reactions.

### References

1. World No Tobacco Day 2026. Available from: <https://www.paho.org/en/campaigns/world-no-tobacco-day-2026>
2. Luo H, et al. Journal of Affective Disorders. 2026;408:121893.
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5. Scheeff S, et al. J. Med. Chem. 2026;69:5501–5539.
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*"Fostering Innovation  
Through Continuous  
Medical Education  
with On the Pulse"*

## Oncology

### **HERNEXEOS®**

(zongertinib)

**BOEHRINGER INGELHEIM**

HK Reg. No. HK-69002 (02 Mar, 2026)

#### **Composition<sup>1</sup>:**

Available as yellow, oval, biconvex, film-coated tablets. Each tablet contains 60 mg of zongertinib

#### **Indication<sup>1</sup>:**

HERNEXEOS® is indicated for the treatment of adult patients with unresectable or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 (ERBB2) tyrosine kinase domain activating mutations, as detected by a validated test, and who have received prior systemic therapy

*ERBB2: Erb-B2 receptor tyrosine kinase 2; HER2: human epidermal growth factor receptor 2*

## Imaging and Diagnosis

### **PRIMOVIST®**

(sodium gadoxetate)

**Liver-specific contrast agent**

**BAYER**

HK Reg. No. HK-69007 (04 Mar, 2026)

#### **Composition<sup>2</sup>:**

Each mL of PRIMOVIST® contains 0.25 mmol disodium gadoxetate. PRIMOVIST® is supplied in 10 mL plastic pre-filled syringes

## Imaging and Diagnosis

### **GADOVIST®**

(gadobutrol)

**Contrast agent**

**BAYER**

HK Reg. No. HK-69019, HK-69020 (12 Mar, 2026)

#### **Composition<sup>3,4</sup>:**

Each mL of GADOVIST® solution for injection contains 1 mmol gadobutrol. GADOVIST® is available in:

- 5 mL plastic prefilled syringes
- 7.5 mL plastic prefilled syringes

Keep Up with the Pace of Drug Development Evolution and Discover the Newly Launched Treatments in Hong Kong

# dexcom G7

Continuous Glucose Monitoring

## REDEFINING DIABETES MANAGEMENT



### Simple to Use<sup>1,2</sup>



#### Small<sup>1</sup>

##### SMALLER PATCH

• 24mm × 27.3mm × 4.6mm



#### Fast<sup>1</sup>

##### FAST WARMUP (<30 MINUTES)

• No need for finger-sticks\*



#### Convenient<sup>1,2</sup>

##### ALL-IN-ONE SENSOR

- Painless<sup>#</sup> to apply<sup>2</sup>
- Smartwatch compatibility<sup>1</sup>
- Remote data sharing with caregivers<sup>1</sup>



### High Accuracy<sup>3-5</sup>



#### Among the lowest reported MARD values (8.2%)

compared with selected commercially available CGMs<sup>4,†</sup>



8.2%  
Adults



8.1%  
Children

### Reliable Treatment Decisions Lead to Proven Results<sup>2,6-10</sup>



>1%  
A1c reduction<sup>10†</sup>



More time  
in range<sup>2,6-9</sup>



Lower  
hyper- and hypo-glycemia<sup>2,6-9</sup>

\*Finger-sticks are required for diabetes treatment decisions if symptoms or expectations do not match readings.

<sup>†</sup>Participants reported on a questionnaire that 94% of sensor insertions felt painless (mild, no pain).

<sup>#</sup>Sensors worn on the back of the upper arm.

<sup>†</sup>Based on MARD values reported for selected commercially available CGM systems. Commercially available CGMs considered include: Dexcom (MARD 8.2%), Abbott FreeStyle Libre 2 Plus (8.2%), Medtronic Guardian™ 4 (10.6–10.8%), Roche Accu-Chek (9.24%), Sibionics GS1 (8.7–8.83%), Sinocare iCan i3/i6 (8.71%), Linx (8.66%), and Ottai (8.11%).

<sup>†</sup>Results obtained in a real-world study after 12 weeks of use (N=248).

**Abbreviations:** A1c, glycated hemoglobin; CGM, continuous glucose monitoring; MARD, mean absolute relative differences.

**References:**1. 1. Dexcom G7 User Guide, 2024. 2. Welsh JB, et al. J Diabetes Sci Technol. 2024;18(1):143-7. 3. Dexcom, Data on File, 2026. 4. Garg SK, et al. Diabetes Technol Ther. 2022;24:373-80. 5. Laffel LM, et al. J Diabetes Sci Technol. 2023;17(4):962-7. 6. Beck RW, et al. JAMA. 2017;317(4):371-8. 7. Beck RW, et al. Ann Intern Med. 2017;167(6):365-74. 8. Martens T, et al. JAMA. 2021;325(22):2262-72. 9. Laffel LM, et al. JAMA. 2020;323(23):2388-96. 10. Gilbert TR, et al. Diabetes Technol Ther. 2021;23(S1):S35-S39.



## Oncology

**ITOVEBI®**

(inavolisib)

**ROCHE**

HK Reg. No. HK-69042, HK-69043 (30 Mar, 2026)

**Composition<sup>5</sup>:**

ITOVEBI® is available as tablets in two dose strengths:

- 3 mg: red and round convex-shaped with an “INA 3” debossing on one side
- 9 mg: pink and oval-shaped with an “INA 9” debossing on one side

**Indication<sup>5</sup>:**

ITOVEBI® (inavolisib film-coated tablets), in combination with palbociclib and fulvestrant, is indicated for:

- the treatment of adult women with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine treatment

## References

1. HERNEXEOS Hong Kong Prescribing Information. 2. Hong Kong Drug Office. PRIMOVIST SOLUTION FOR INJECTION IN PLASTIC PRE-FILLED SYRINGE 0.25 MMOL/ML 10ML. Available from: [https://www.drugoffice.gov.hk/eps/drug/productDetail/en/pharmaceutical\\_trade/159313](https://www.drugoffice.gov.hk/eps/drug/productDetail/en/pharmaceutical_trade/159313). [Accessed 21 May 2026]. 3. Hong Kong Drug Office. GADOVIST SOLUTION FOR INJECTION IN PLASTIC PRE-FILLED SYRINGE 1MMOL/ML 5ML. Available from: [https://www.drugoffice.gov.hk/eps/drug/productDetail/en/pharmaceutical\\_trade/159484](https://www.drugoffice.gov.hk/eps/drug/productDetail/en/pharmaceutical_trade/159484). [Accessed 21 May 2026]. 4. Hong Kong Drug Office. GADOVIST SOLUTION FOR INJECTION IN PLASTIC PRE-FILLED SYRINGE 1MMOL/ML 7.5ML. Available from: [https://www.drugoffice.gov.hk/eps/drug/productDetail/en/pharmaceutical\\_trade/159485](https://www.drugoffice.gov.hk/eps/drug/productDetail/en/pharmaceutical_trade/159485). [Accessed 21 May 2026]. 5. ITOVEBI Hong Kong Prescribing Information.

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We would like to clarify that the Afatinib Sandoz information published in the 35<sup>th</sup> issue (April 2026) of V.Pulse was neither provided by, reviewed by, authorised by, nor approved by Sandoz.

