Spravato®
(esketamine)
nasal spray

速開朗®

針對谷氨酸帶來新希望

30年來首個獲認可的抗抑鬱藥運作原理[1-6,*,†]

*SPRAVATO® 速開朗®適用於患有難治性重度抑鬱症，在當前的中度至重度抑鬱發作中對至少兩種不同抗抑鬱藥治療反應不足的成年人。SPRAVATO® 速開朗®須與SSRI或SNRI一同使用[1]。

†在1987年開發和批准SSRI fluoxetine後，批准的治療方法（包括非典型抗抑鬱藥，如mirtazapine, agomelatine等）皆專注於單胺系統或至少對單胺系統產生一些影響[2,5]。

本小冊子僅供醫護人員使用和作參考用途。

抑鬱症現況小檔案

現時全球十大疾病負擔中
排名第三[7]

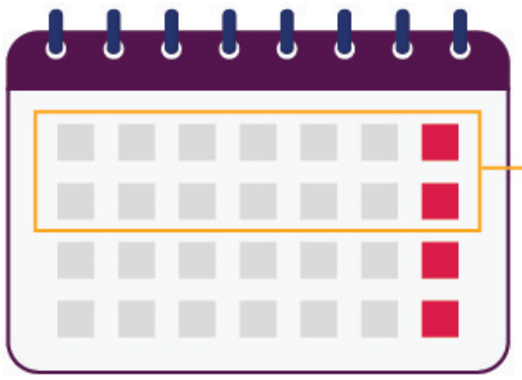
2030年預計成為
全球第1疾病負擔[7,8]

超過**30萬香港人**
患有抑鬱症[9]

抑鬱症帶有什麼症狀[10]？

如在2週內，患者幾乎大部分時間都出現下列≥5個症狀（當中包括情緒低落或失去興趣或樂趣），
則可被診斷患有抑鬱症。

2週內



≥5個症狀

- 情緒低落*
- 對所有或幾乎所有活動的興趣或樂趣明顯減少*
- 體重或食慾都出現明顯增加或減少†
- 思想動作變得緩慢（其他人可以觀察到，不僅僅是煩躁或放慢的主觀感覺）‡
- 失眠或嗜睡‡
- 感到疲倦‡
- 感到自身無價值（過度或不適當的內疚感）‡
- 思考或集中注意力的能力下降，或優柔寡斷‡
- 反覆出現自殺意念

*幾乎每一天的大部分時間　†食慾：幾乎每一天；體重：一個月內改變5%　‡幾乎每一天
在本小冊子中，「抑鬱症」意指重度抑鬱症。

殘餘症狀：未完全從抑鬱症康復的指標

不少患者雖然正在接受藥物治療，但病情未得到完全緩解。他們很大機會出現不同精神上及身體上的殘餘症狀[11]。
常見症狀包括[11,12]：

情緒影響	身體影響	日常生活影響
☐ 情緒持續低落	☐ 失眠	☐ 對身邊事物失去興趣
☐ 感到內疚	☐ 性慾降低	☐ 對工作失去興趣
☐ 焦慮	☐ 背痛	☐ 工作表現下降
☐ 容易發怒	☐ 肌肉痛	☐ 認知功能障礙
☐ 時常感到疲倦	☐ 胃痛	
	☐ 關節疼痛	

殘餘症狀令復發風險大大增加[12]

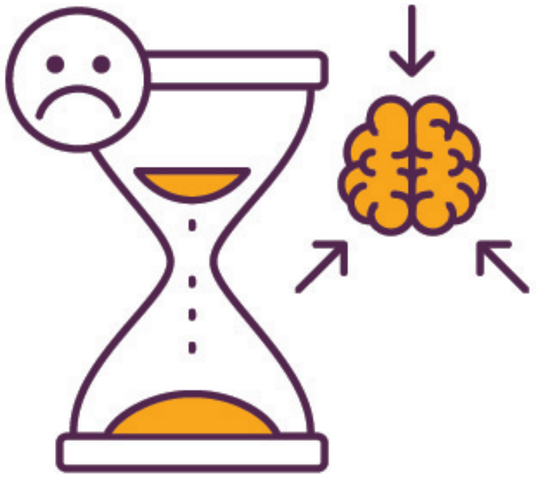
出現殘餘症狀的患者有需要調整現時的抑鬱治療方案，以防止復發。

在本小冊子中，「抑鬱症」意指重度抑鬱症。

抑鬱症復發對患者的腦部影響

研究顯示，抑鬱症患者腦部受到慢性炎症影響，導致大腦結構和功能出現變化。而更長時間和更頻繁的抑鬱發作將令患者的功能加速衰退[13,14]。

復發患者的島葉體積和背外側前額葉體積顯著下降[15]

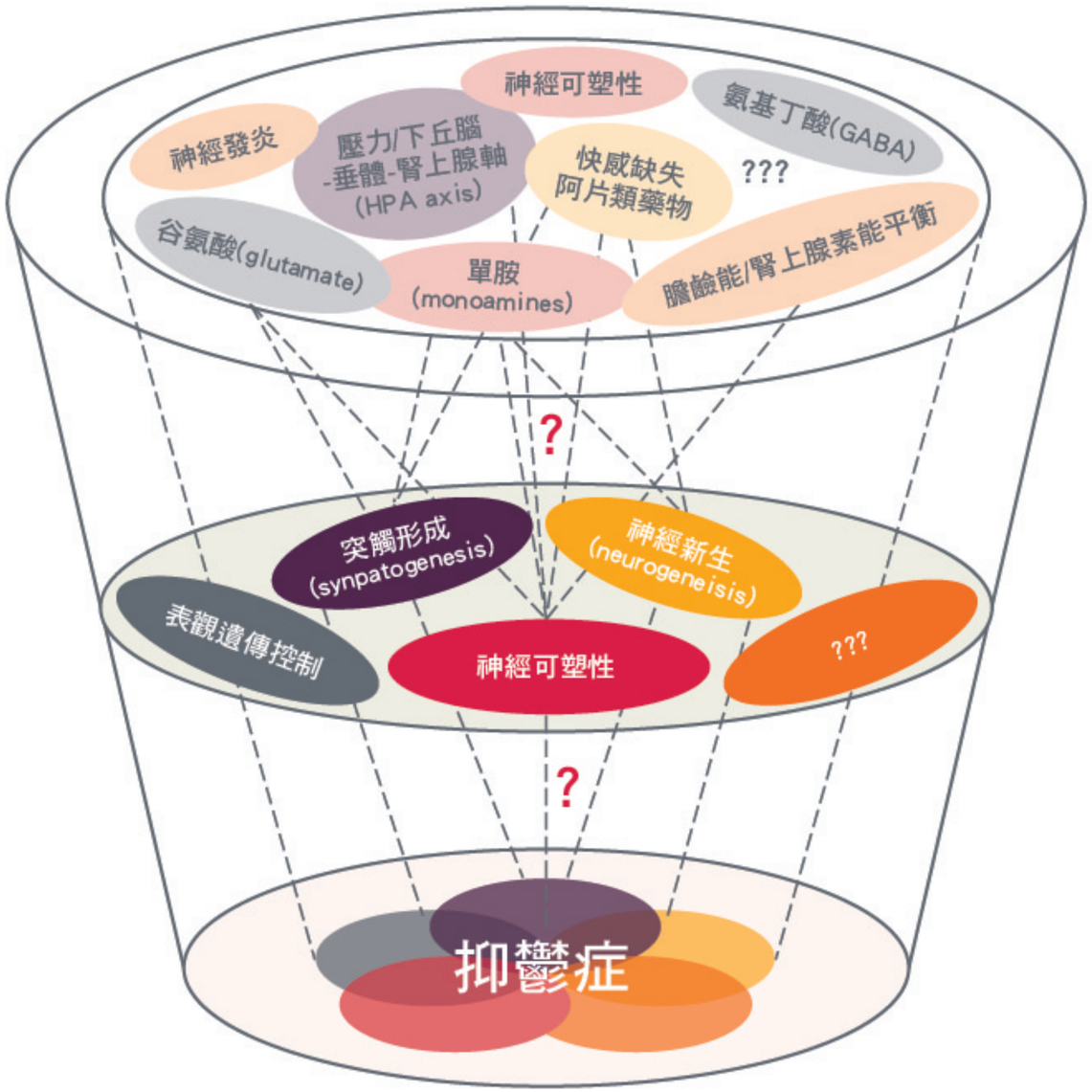


腦部體積收縮與抑鬱症發作次數成正比[14]

記憶力下降和出現癡呆的風險隨著抑鬱發作的次數而增加[14]

在本小冊子中，「抑鬱症」意指重度抑鬱症。

更多藥物選擇 · 針對不同成因



由於抑鬱症的成因複雜，沒有單一的病理機制可以充分解釋每位抑鬱症患者的發病原因[16]。

然而，過去30年的抗抑鬱藥物僅針對單胺系統(monoamine)，運作原理未能顧及其他可能的病理成因[2-5]。不少部分抑鬱症病人亦未能透過服用以往的抗抑鬱藥物達到緩解[17,18]。

達到完全緩解 和
消除所有抑鬱症狀
為抑鬱症的治療目標[19,20]

現時，醫學界積極開發針對其他系統的新抗抑鬱藥物，當中包括針對谷氨酸系統(glutamate)的藥物[16]。

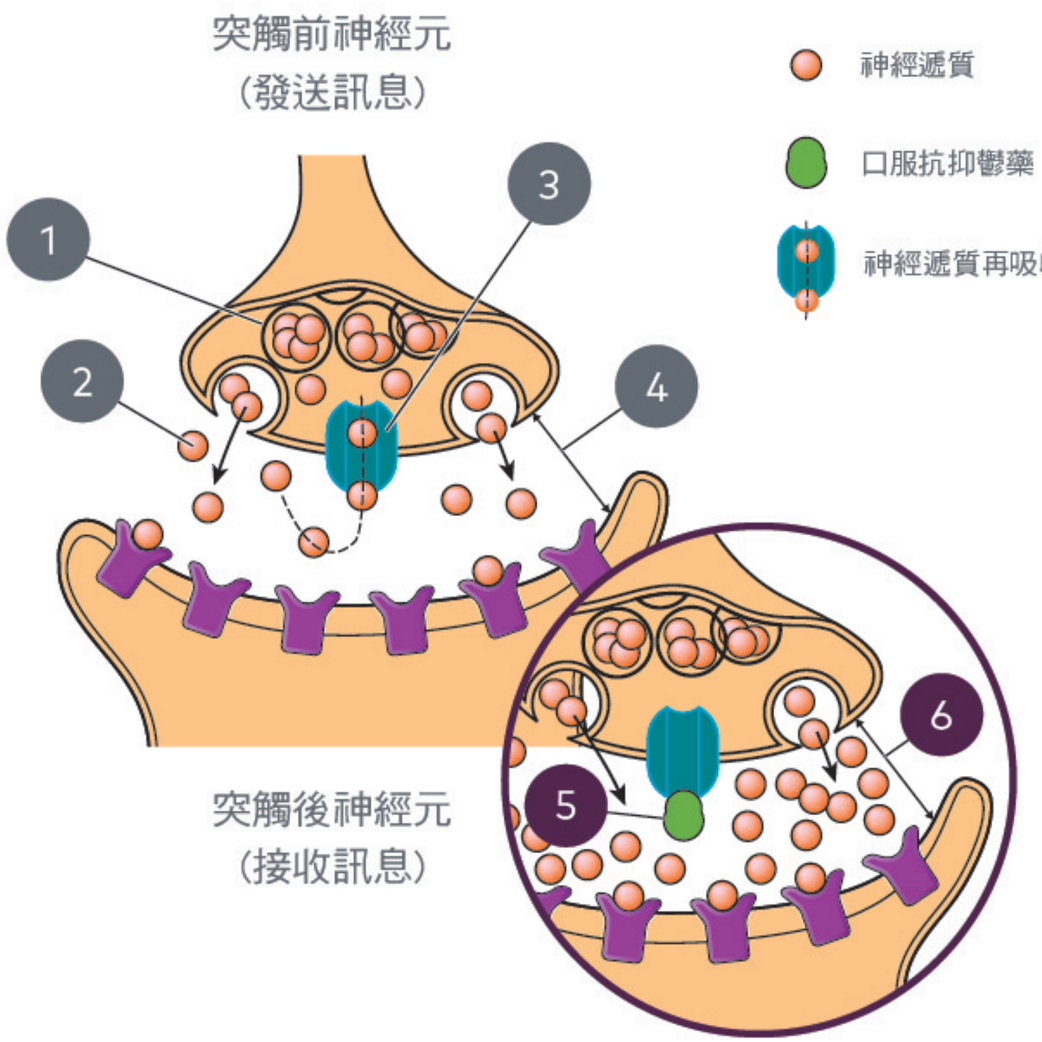
透過雙管齊下的藥物治療方案，患者有望在更短時間內減輕抑鬱情緒，得到緩解[6]。

在本小冊子中，「抑鬱症」意指重度抑鬱症。

傳統的口服抗抑鬱藥: 針對單胺系統

起效時間
4-6星期[33]

過去數十年，抑鬱症研究專注於單胺假說，其提出抑鬱症患者的單胺類神經遞質水平出現失衡，當中包括**血清素**、**去甲腎上腺素**和**多巴胺**[2]。市面上大部分口服抗抑鬱藥的運作原理皆針對單胺系統，透過提升單胺水平以改善患者情況[21]。



神經遞質

口服抗抑鬱藥

神經遞質再吸收

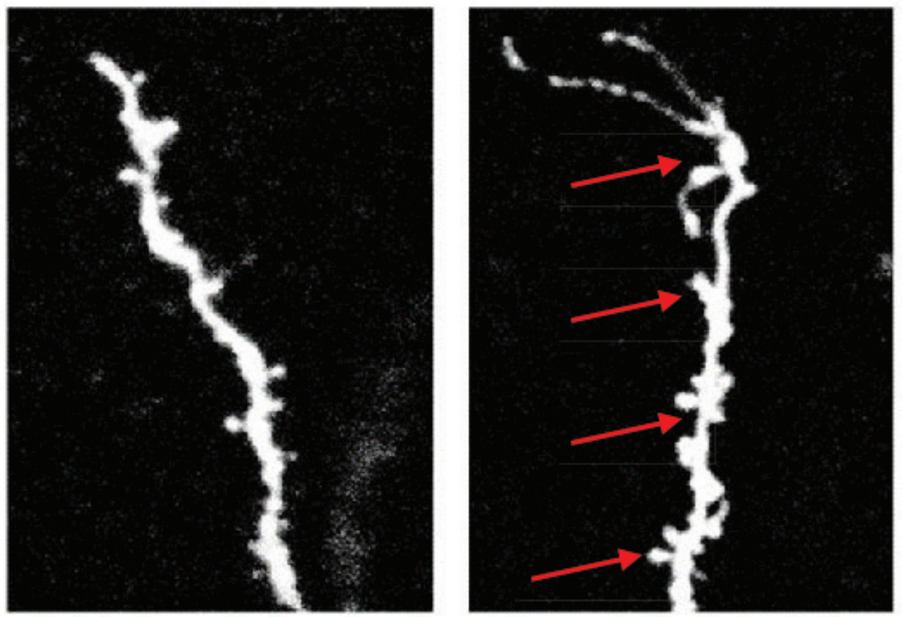
1	神經遞質處於神經細胞的囊泡，負責聯繫神經元[22]
2	神經遞質從一條神經的末端釋放並被另一條神經接收[22]
3	當中部分神經遞質會被再吸收(reuptake)[22]
4	由於患者的大腦神經遞質低於正常水平，在再吸收的情況下，神經元之間的神經遞質濃度變得過低，影響訊息傳遞，導致抑鬱症狀[22]
5	口服抗抑鬱藥，例如SSRI和SNRI，採用抑制原理，令被再吸收的神經遞質減少[22,23]
6	大腦神經周圍的神經遞質濃度得以提升[22]

SSRI=血清素再吸收抑制劑; SNRI=血清素及去甲腎上腺素再吸收抑制劑
在本小冊子中，「抑鬱症」意指重度抑鬱症。

針對谷氨酸系統 · 為患者帶來新希望

谷氨酸(glutamate)為中樞神經系統中主要的興奮性神經遞質，在大腦一半以上的神經元連接中擔當著重要角色[24]。

近年研究發現，抑鬱症患者的谷氨酸信號傳遞出現異常，令大腦中部分關鍵區域的神經元之間大腦的連接量和強度下降，繼而影響情緒控制[25]。



對照組別　　治療組別

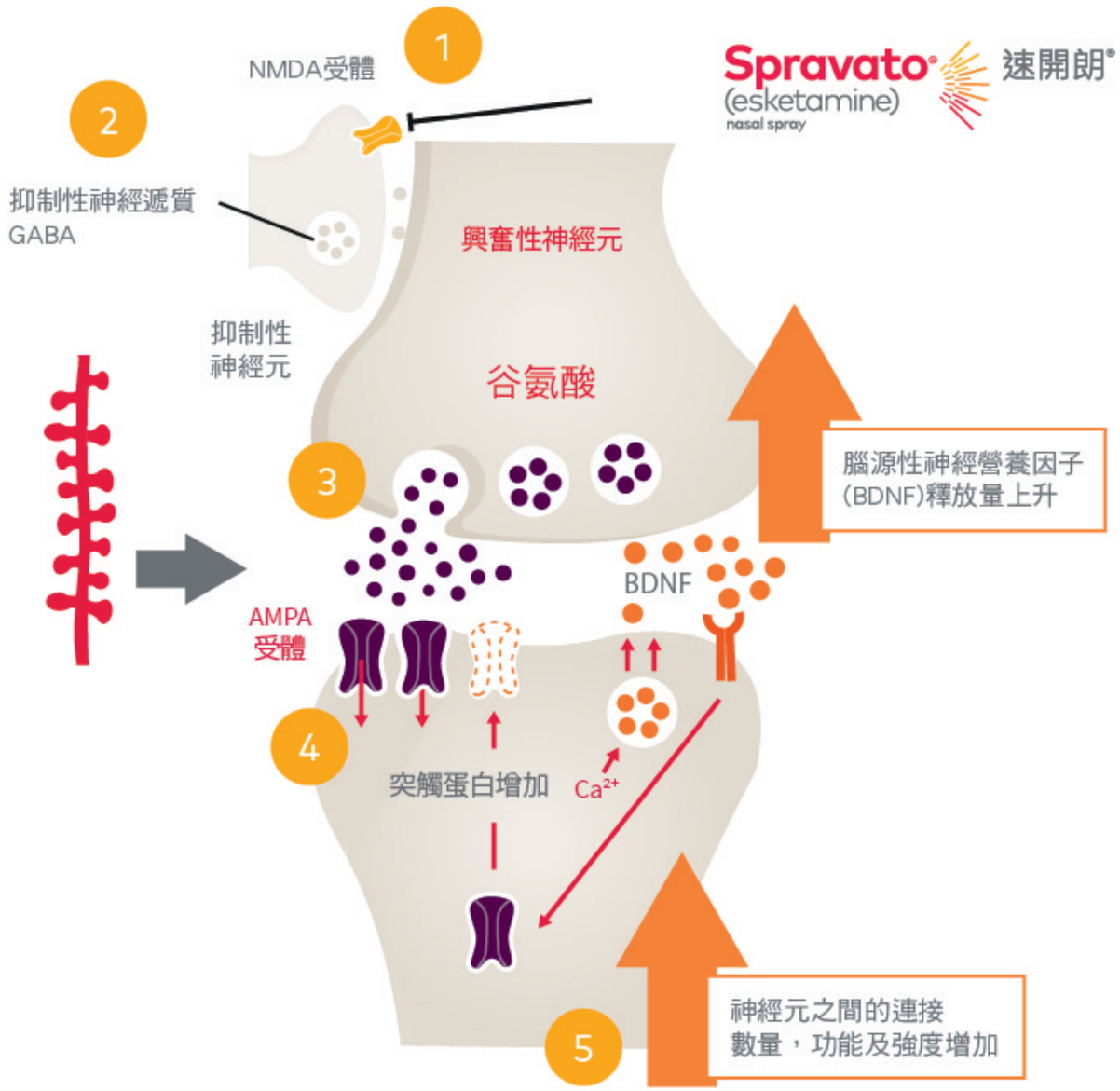
透過阻斷一種稱為NMDA受體的谷氨酸受體，SPRAVATO® 速開朗® 相信能增加谷氨酸釋放，改善腦神經元之間的連接表現[25]。

研究顯示，在使用谷氨酸受體調節劑後24小時內，大腦神經元之間的連接數量有所增加和強度提升[26,‡]。

*SPRAVATO® 速開朗® 適用於患有難治性重度抑鬱症，在當前的中度至重度抑鬱發作中對至少兩種不同抗抑鬱藥治療反應不足的成年人。SPRAVATO® 速開朗® 須與SSRI 或SNRI一同使用[1]。
†在1987年開發和批准 SSRI fluoxetine後，批准的治療方法（包括非典型抗抑鬱藥，如 mirtazapine, agomelatine等）皆專注於單胺系統或至少對單胺系統產生一些影響[2-5]。
‡臨床前數據

SPRAVATO® 速開朗® 的運作原理

SPRAVATO® 速開朗® 含有活性物質esketamine，為一種NMDA受體拮抗劑，運作原理以谷氨酸系統為本[1]。



Spravato® (esketamine) nasal spray 速開朗®

1	SPRAVATO® 速開朗® 黏附著NMDA受體[25]
2	阻斷NMDA受體導致谷氨酸大量釋放[25]
3	谷氨酸繼而激活AMPA受體[25]
4	所引發的一連串細胞活動有助增加神經元之間的信號傳遞[25]
5	大腦區域中神經的連接得以增強，有助改善患者的情緒控制[25]

SPRAVATO® 速開朗® 如何幫助難治型抑鬱症患者？

SPRAVATO® 速開朗® 適用於以往嘗試過至少2種其他抗抑鬱藥物，但病情未能得到緩解的成年患者（難治型抑鬱症患者）[1]。

運作原理

SPRAVATO® 速開朗® 為30年來首款以谷氨酸系統為本的抗抑鬱藥物，運作原理有別於過去數十年針對單胺系統的藥物[1-6,*,†]。

雙重運作原理治療方案

SPRAVATO® 速開朗® 與口服抗抑鬱藥合用，兩者針對抑鬱症不同的病理成因，以達到更佳的治療效果[1]。

獨特噴鼻形式

SPRAVATO® 速開朗® 為噴鼻劑。噴鼻形式讓藥物能被鼻粘膜的血管床快速吸收，藥物起效更爲迅速[27]。

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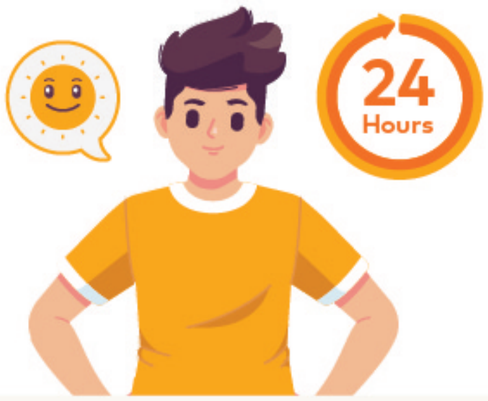
†在1987年開發和批准 SSRI fluoxetine後，批准的治療方法（包括非典型抗抑鬱藥，如 mirtazapine, agomelatine等）皆專注於單胺系統或至少對單胺系統產生一些影響[2-5]。

SPRAVATO® 速開朗® 如何幫助難治型抑鬱症患者？



24小時起效[6]

(SPRAVATO® 速開朗® +口服抗抑鬱藥的患者最快能在24小時內減輕抑鬱症狀)

一半以上患者在第28天達到緩解期[6]

(SPRAVATO® 速開朗® +口服抗抑鬱藥：52.5% vs 安慰劑+口服抗抑鬱藥：31.0%)

長期降低70%復發風險[28]

(穩定反應的患者, HR=0.30, 95% CI 0.16-0.55; P<0.001)

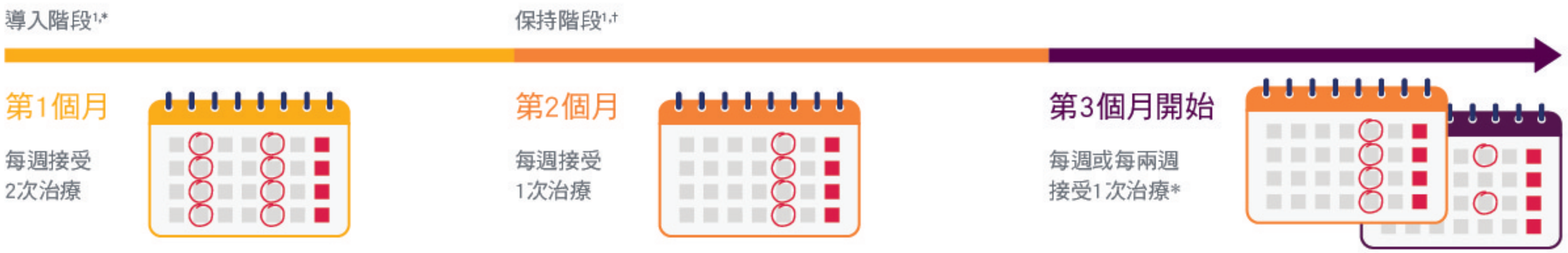
一年後58.2%患者仍能保持在緩解期[29]

(n=351/603)

反應：指在持續服用適當劑量的抗抑鬱藥後，MADRS評分減少50%或以上；緩解：指在持續服用適當劑量的抗抑鬱藥後，MADRS評分降至12分或以下[28]

*在單次給藥後24 小時，治療組之間的平均 MADRS 評分差異為 -3.3 分[6]。臨床定義上，與安慰劑最少具意義的差異為總 MADRS 評分降低≥1.6[30]。TRANSFORM-2 為第3期臨床研究，當中有 227 名患有中度至重度抑鬱症且在當前發作中對至少兩種抗抑鬱藥無反應的成年人參與。 確認的無反應者被隨機分配接受 4 週 SPRAVATO® 速開朗®（56 或 84 mg，每週兩次）和一種抗抑鬱藥，或一種抗抑鬱藥和安慰鼻噴霧劑的治療。 主要療效量度為 MADRS 評分從基線到第 28 天 的變化[6]。

SPRAVATO® 速開朗® 療程時間表



- 根據患者情況，如有需要，醫生可於每次療程相應減少或增加劑量，以維持治療反應[1]。
- 如果錯過了一個或兩個療程，患者應按照現時治療頻率安排下一個療程。如果錯過了超過 2 個療程，醫生則可能需要根據臨床判斷，調整患者SPRAVATO® 速開朗® 的劑量或療程頻率[1]。

*應在導入期結束時評估治療成效，以判斷患者是否需要繼續接受治療。
†應定期重新患者評估是否需要繼續治療，並因應患者個人情況而調整至最低的給藥頻率以維持緩解/反應。

接受SPRAVATO® 速開朗® 療程前患者的注意事項[1]

療程前2小時內
請勿進食

療程前1小時內請避免使
用鼻用類固醇或通鼻劑

療程前30分鐘內
請勿飲用液體

因接受療程後不適宜駕駛、操作機器或進行任何需高度專注的活動，
請提醒患者預先安排照顧者接送或考慮乘搭公共交通工具離開療程中心。

SPRAVATO® 速開朗® 使用步驟

使用指南影片

步驟 1 事前準備[1]

使用第一個裝置之前:

- 請患者擤清鼻腔，僅於**第一劑之前需要**

- 確定所需裝置數量
(56mg=兩個裝置; 84mg=三個裝置)*

步驟 2 準備裝置[1]

- 檢查有效期限 (EXP)
- 如已過期，請使用新裝置
- 拆開包裝，取出裝置

- 請勿預先按壓藥劑，這會導致藥劑溢出
- 確定噴出記號顯示**2個綠點**
- 若不符，請丟棄裝置並使用新裝置

步驟 3 準備患者[1]

指導患者:

- 如圖握住裝置，用拇指輕托柱塞
- 請先不要按壓柱塞

指導患者:

- 頭向後仰約45度，以確保使用時藥劑留在鼻內

*65 歲或以上患者可能需要使用28mg(1個裝置)劑量

步驟 4　患者每個鼻孔噴一下[1]

指導患者:

- 將噴嘴直立放入一側鼻孔內
- 鼻托應接觸兩鼻孔之間的皮膚

指導患者:

- 用手壓住另一側鼻孔
- 用鼻吸氣，向上將柱塞壓到底，使之噴出指定劑量

指導患者:

- 噴完請輕輕吸氣，
  盡量讓藥劑留在鼻內

指導患者:

- 換手，將噴嘴放入另一側鼻孔
- 重複步驟4噴第二次

步驟 5　確認患者吸入藥劑後休息[1]

- 取回患者的裝置
- 確定噴出記號顯示無綠點。
  若顯示綠點，請患者將藥劑
  重新噴入第二次的鼻孔內
- 鼻托應接觸兩鼻孔之間的皮膚

指導患者:

- 在使用每個裝置後以舒服的姿勢
  (建議半斜躺)休息5分鐘
- 鼻托應接觸兩鼻孔之間的皮膚

⚠ 請勿擤鼻

- 重複步驟2至5操作下個裝置

確保每個患者在使用每個裝置後休息5分鐘，讓藥劑吸收。

SPRAVATO® 速開朗® 的安全性如何？

耐受性良好

在臨床研究中，使用SPRAVATO® 速開朗® 口服抗抑鬱藥的患者當中

- 只有3.8%（n=23/603）的患者在48周因爲出現副作用而停藥[29]
- 沒有證據顯示患者出現與濫用藥物相關的副作用[28]
- 沒有證據顯示患者在停止服用SPRAVATO® 的首兩星期出現戒斷綜合徵狀[28]

常見的不良反應為：


頭暈


噁心


解離


頭痛


嗜睡


眩暈


味覺障礙


感覺減退


嘔吐


這些副作用一般只會持續短時間[1,6]

SPRAVATO® 速開朗® 的安全性如何？

妥善風險管理

- 接受SPRAVATO® 速開朗® 後，患者可能會出現嗜睡和解離狀況。醫護人員應對患者進行監測，直到認為患者臨床情況穩定，便可讓其離開診所[1]。

- SPRAVATO® 速開朗® 可導致血壓升高，不過只屬短暫現象，普遍持續約 1-2 小時[1]。
- 在開始療程之前，醫生應確保患者的血壓屬於正常水平[1]。
- 醫護人員應在用藥後40分鐘為患者量度血壓，隨後根據臨床需要定時進行量度，直到血壓回復正常[1]。

SPRAVATO® 速開朗® 問與答

有什麼患者不適合使用SPRAVATO® 速開朗®[1]？

如患者有下列情形，請勿使用SPRAVATO® 速開朗®

- 對於本藥物中的任何其他成分過敏
- 血壓或顱內壓升高會帶來嚴重風險，包括患有動脈瘤（血管壁上的薄弱部位變寬或凸出）、腦出血、近期有心臟病發作（6 週以內）的患者

如果患者現正懷孕，並不建議使用SPRAVATO® 速開朗®

- 如果患者在使用SPRAVATO® 速開朗® 期間懷孕，應立刻通知醫生以便其判斷是否應該停止治療，或採取其他治療

如患者有以下任何一種症狀，其應只在利益大於風險的情況下使用SPRAVATO® 速開朗®

- 血流動力學顯著的心臟瓣膜病或心臟衰竭
- 曾經有過心跳緩慢或心跳加快，導致呼吸急促、血流動力學不穩定
- 曾經有過大腦血液供應問題（例如中風）
- 頭部曾經腦部受損、高血壓性腦病變、心室分流鞘內治療或任何其他與顱內壓升高有關的疾病
- 曾經有過藥物濫用或酗酒問題
- 曾經患有精神病疾病，出現妄想或幻覺
- 曾經患有雙相情感障礙或躁狂症狀（過度活躍或過度興奮）
- 曾經患有甲狀腺功能亢進症，未經適當治療（甲狀腺功能亢進）
- 曾經患有引起呼吸困難的肺部疾病（肺功能不全），包括慢性阻塞性肺病（COPD）
- 睡眠窒息症和體重嚴重超重

SPRAVATO® 速開朗® 問與答

有甚麼機制能確保SPRAVATO® 速開朗® 在安全的情況下使用，減低濫用風險？

化學結構

為 esketamine（左外旋體），對 NMDA 受體的親和力(affinity)比arketamine高[31]

獲得認可

經過多個臨床研究驗證，並獲香港醫管局認可用於抑鬱症治療[6,28,29,32]

低劑量

使用劑量低而且不頻繁；在最頻繁的導入階段，患者亦僅建議每週用藥兩次，每次28-84毫克[1]

妥善監管

為處方藥物，患者僅能於診所內在醫療人員監督下使用SPRAVATO® 速開朗®，無法自行在家中使用[1]

SPRAVATO® 速開朗® 問與答

高血壓患者可以使用SPRAVATO® 速開朗®嗎[1]？

若患者的基線血壓過高（65歲以下患者: >140/90 mmHg；≥ 65歲或以上患者 >150/90 mmHg），其應只在利益大於風險的情況下使用SPRAVATO® 速開朗®。醫生可建議高血壓患者透過改善生活習慣以降低血壓，以確保其狀況適合接受SPRAVATO® 速開朗® 治療。

接受SPRAVATO® 速開朗®療程後，可以上班嗎[1]？

用藥過後, 醫生會觀察患者一段時間，以了解患者是否受副作用影響。在臨床試驗中，大部分人可以在使用SPRAVATO® 速開朗® 90分鐘後離開診所。接受療程後患者不適宜駕駛、操作機器或進行任何需高度專注的活動，患者可視乎工作性質，並咨詢醫生其身體狀況是否適合上班工作。

SPRAVATO® 速開朗® 出現濫用或導致膀胱問題的風險高嗎[28,29]？

- 在臨床試驗中，沒有證據顯示患者有濫用SPRAVATO® 速開朗® 的行為或在停止治療兩星期後出現戒斷綜合徵狀。
- 沒有患者要求增加劑量或給藥頻率。
- 在長達48周的臨床試驗中，沒有出現間質性膀胱炎的病例。泌尿系統症狀的發生率低，而且一般為輕度至中度，並在 2 週內消失。
- 在處方SPRAVATO® 速開朗® 之前，醫生應評估每位患者的濫用或誤用風險，包括其有否藥物濫用或依賴史。

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SPRAVATO®

ABBREVIATED PRESCRIBING INFORMATION

ACTIVE INGREDIENT(S): esketamine (as hydrochloride) INDICATION(S): Spravato, in combination with a SSRI or SNRI, is indicated for adults with treatment-resistant Major Depressive Disorder, who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode. Spravato, co-administered with oral antidepressant therapy, is indicated in adults with a moderate to severe episode of Major Depressive Disorder, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency. DOSAGE & ADMINISTRATION: The decision to prescribe Spravato should be determined by a psychiatrist. Spravato is intended to be self-administered by the patient under the direct supervision of a healthcare professional. Assessment before treatment - Prior to dosing with Spravato blood pressure should be assessed. Post-administration observation - After dosing with Spravato, blood pressure should be reassessed at approximately 40 minutes and subsequently as clinically warranted. Recommended dosing for Spravato in adults <65 years with treatment-resistant Major Depressive Disorder - Induction phase, Weeks 1-4: Starting day 1 dose: 56 mg; Subsequent doses: 56 mg or 84 mg twice a week); Maintenance phase, Weeks 5-8: 56 mg or 84 mg once weekly; From Week 9: 56 mg or 84 mg every 2 weeks or once weekly. Recommended dosing for Spravato in adults ≥65 years with treatment-resistant Major Depressive Disorder - Induction phase, Weeks 1-4: Starting day 1 dose: 28 mg; Subsequent doses: 28 mg, 56 mg or 84 mg twice a week* ; Maintenance phase, Weeks 5-8: 28 mg, 56 mg or 84 mg once weekly* ; From Week 9: 28 mg, 56 mg or 84 mg every 2 weeks or once weekly* (*All dose changes should be in 28 mg increments.) Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment. The need for continued treatment should be reexamined periodically. After depressive symptoms improve, treatment is recommended for at least 6 months. Acute short-term treatment of psychiatric emergency due to Major Depressive Disorder - Recommended dosage of Spravato for adult patients (<65 years) is 84 mg twice per week for 4 weeks. Dosage reduction to 56 mg should be made based on tolerability. After 4 weeks of treatment with Spravato, the oral antidepressant (AD) therapy should be continued, per clinical judgement. Patients should be advised not to eat for at least 2 hours before administration and not to drink liquids at least 30 minutes prior to administration. Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should be advised not to administer these medicinal products within 1 hour before Spravato administration. Patients who have missed treatment session(s) during the first 4 weeks of treatment should continue with their current dosing schedule. For patients with treatment-resistant Major Depressive Disorder who miss treatment session(s) during maintenance phase and have worsening of depression symptoms, per clinical judgement, consider returning to the previous dosing schedule. Efficacy of Spravato in Japanese patients has been studied, but not established. Method of administration - For nasal use only. Do not prime before use. CONTRAINDICATIONS: Hypersensitivity to the active substance, ketamine, or to any of the excipients listed in the full prescribing information. Patients for whom an increase in blood pressure or intracranial pressure poses a serious risk: Patients with aneurysmal vascular disease (including intracranial, thoracic, or abdominal aorta, or peripheral arterial vessels); Patients with history of intracerebral haemorrhage; Recent (within 6 weeks) cardiovascular event, including myocardial infarction (MI). SPECIAL WARNINGS & PRECAUTIONS: Suicide/suicidal thoughts or clinical worsening - Effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behaviour has not been demonstrated. Use of Spravato does not preclude the need for hospitalisation if clinically warranted, even if patients experience improvement after an initial dose of Spravato. Close supervision of patients especially in early treatment and following dose changes. Patients and caregivers should be alerted to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment. Neuropsychiatric and motor impairments - Spravato has been reported to cause somnolence, sedation, dissociative symptoms, perception disturbances, dizziness, vertigo and anxiety during the clinical trials. At each treatment session, patients should be monitored under the supervision of a healthcare professional to assess when the patient is considered stable based on clinical judgement. Respiratory depression - Respiratory depression may occur at high doses following rapid intravenous injection of esketamine or ketamine when used for anaesthesia. Close monitoring is required for sedation and respiratory depression. Effect on blood pressure - Spravato can cause transient increases in systolic and/or diastolic blood pressure which peak at approximately 40 minutes after administration of the medicinal product and last approximately 1-2 hours. A substantial increase in blood pressure could occur after any treatment session. Spravato is contraindicated in patients for whom an increase in blood pressure or intracranial pressure poses a serious risk. Before prescribing Spravato, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of Spravato outweigh its risks. In patients whose blood pressure prior to dose administration is judged to be elevated, it is appropriate to adjust lifestyle and/or pharmacologic therapies to reduce blood pressure before starting treatment with Spravato. If blood pressure is elevated prior to Spravato administration a decision to delay Spravato therapy should take into account the balance of benefit and risk in individual patients. Blood pressure should be monitored after dose administration. Blood pressure should be measured around 40 minutes post-dose and subsequently as clinically warranted until values decline. If blood pressure remains elevated for a prolonged period of time, assistance should promptly be sought from practitioners experienced in blood pressure management. Patients who experience symptoms of a hypertensive crisis should be referred immediately for emergency care. Patients with clinically significant or unstable cardiovascular or respiratory conditions - Only initiate treatment with Spravato in patients with clinically significant or unstable cardiovascular or respiratory conditions if the benefit outweighs the risk. Spravato should be administered in a setting where appropriate resuscitation equipment and healthcare professionals with training in cardiopulmonary resuscitation are available. Refer to the full prescribing information for examples of conditions. Drug abuse, dependence, withdrawal - Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of Spravato. Prior to prescribing Spravato, each patient's risk for abuse or misuse should be assessed and patients receiving esketamine should be monitored for the development of behaviours or conditions of abuse or misuse, including drug seeking behaviour, while on therapy. Dependence and tolerance have been reported with prolonged use of ketamine. In individuals who were dependent on ketamine, withdrawal symptoms of cravings, anxiety, shaking, sweating and palpitations have been reported upon discontinuing ketamine. Ketamine, the racemic mixture of arketamine and esketamine, is a medicinal product that has been reported to be abused. The potential for abuse, misuse and diversion of Spravato is minimised due to the administration taking place under the direct supervision of a healthcare professional. Spravato contains esketamine and may be subject to abuse and diversion. Other populations at risk - Use with caution in patients with the following conditions. These patients should be carefully assessed before prescribing Spravato and treatment initiated only if the benefit outweighs the risk: (i) Presence or history of psychosis; (ii) Presence or history of mania or bipolar disorder; (iii) Hyperthyroidism that has not been sufficiently treated; (iv) History of brain injury, hypertensive encephalopathy, intrathecal therapy with ventricular shunts, or any other condition associated with increased intracranial pressure. Elderly (65 years of age and older) - May have a greater risk of falling once mobilised, therefore, these patients should be carefully monitored. Severe hepatic impairment - Due to expected increase in exposure and lack of clinical experience, Spravato is not recommended in patients with Child-Pugh class C (severe) hepatic impairment. Hepatotoxicity has been reported with chronic ketamine use, so the potential for such an effect due to long-term use of Spravato cannot be excluded. Urinary tract symptoms - Urinary tract and bladder symptoms have been reported with Spravato use. Recommended to monitor for urinary tract and bladder symptoms during the course of treatment and refer to an appropriate healthcare provider when symptoms persist. SIDE EFFECTS: The most commonly observed adverse reactions in treatment resistant depression patients treated with Spravato were dizziness, nausea, dissociation, headache, somnolence, vertigo, dysgeusia, hypoaesthesia, and vomiting. Refer to the full prescribing information for other side effects. PREGNANCY & LACTATION: Spravato is not recommended during pregnancy and in women of childbearing potential not using contraception. There are no or limited data on the use of esketamine in pregnant women. If a woman becomes pregnant while being treated with Spravato, treatment should be discontinued, and the patient should be counselled about the potential risk to the foetus and clinical/therapeutic options as soon as possible. It is unknown whether esketamine is excreted in human milk. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Spravato therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. INTERACTIONS: Concomitant use of Spravato with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation, which therefore should be closely monitored. Blood pressure should be closely monitored when Spravato is used concomitantly with psychostimulants (e.g., amphetamines, methylphenidate, modafanil, armodafinil) or other medicinal products that may increase blood pressure (e.g. xanthine derivatives, ergometrine, thyroid hormones, vasopressin, or MAOIs, such as, tranylcypromine, selegiline, phenelzine). PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING. Spravato aPI ver.2.0

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