Il punto sulla memantina

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Dipartimento Medicina e Riabilitazione,
Istituto Clinico “S. Anna”, Brescia
La memantina nel trattamento delle demenze

ANTAGONISTA NN COMPETITIVO A BASSA AFFINITÀ' PER IL RECETTORE NMDA

Memantina
Glutamate

- The amino acid glutamate is the principal excitatory neurotransmitter of the brain
- Considered to be the main neurotransmitter of neocortical and hippocampal pyramidal neurones
- Involved in higher mental functions such as cognition and memory
- The majority of neurones, and indeed glia, are likely to be influenced by glutamate since they have receptors for glutamate

Glutamate–glutamine cycle

- Glutamate
- Glutamine
- NMDA receptor

Glutamatergic pyramidal neurone

Astroglial cell

VGluT

Low noise

Ca²⁺

Signal

HIGH PEAK

LOW BACKGROUND

ATP

Postsynaptic pyramidal neurone
Actions of glutamate

- Beneficial
  - Long-term potentiation (LTP), NMDA and AMPA signalling
  - Neuroprotection (indirect action)

- Potentially harmful
  - Excitotoxicity (exogenous and endogenous)
Glutamate in AD

- Glutamate uptake is reduced in frontal/temporal cortex
- Selective loss of vesicular glutamate transport
- Reduced number of NMDA receptor subunits in the hippocampus – reduced NMDA function
- Signalling between cortical areas and hippocampus is dysfunctional
- $\beta$-amyloid, like glutamate, decreases signal-to-noise ratio in AD and impairs cognition
Sistema glutamatergico e Aβ

- Aβ
  - ADDL’s (oligomeri solubili di Aβ)
  - Legame a NMDA o in sua prossimità
  - ↑ Ca2+ intracellulare
  - ↑ ROS

Memory Loss
Memantine

- Memantine is a moderate-affinity NMDA receptor antagonist, blocking the associated ion channel
- Voltage-dependent, similar to Mg\(^{2+}\)
- Permits Long Term Potentiation (LTP) – ‘learning’
- Prevents excessive Ca\(^{2+}\) influx
- Reduces ‘noise’ and hence improves signal-to-noise ratio

MEMANTINA

ANTAGONISTA NON COMPETITIVO A BASSA AFFINITA’ RecNMDA

blocco attivazione tonica di bassa intensità di NMDA senza interferire con la sua attivazione fasica (necessaria per apprendimento e memorizzazione)

NEUROPROTEZIONE

EFFETTI SU PLASTICITA’ SINAPTICA, FUNZIONI MNESICHE E APPRENDIMENTO
# Memantine Phase III, placebo-controlled, clinical studies in AD

<table>
<thead>
<tr>
<th>Study No. (Author)</th>
<th>MMSE inclusion Range (Mean)</th>
<th>Duration/Design</th>
<th>Number of treated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD-10 (Peskind)</td>
<td>10–22 (17.3)</td>
<td>24-week/DB, PBO-controlled</td>
<td>403</td>
</tr>
<tr>
<td>99679 (Bakchine)</td>
<td>11–23 (18.7)</td>
<td>24-week/DB, PBO-controlled</td>
<td>470</td>
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<tr>
<td>MD-12 (Clinical trial registry)</td>
<td>10–22 (16.9)</td>
<td>24-week/DB, PBO-controlled in patients already receiving donepezil, rivastigmine, or galantamine</td>
<td>433</td>
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<tr>
<td>MRZ-9605 (Reisberg)</td>
<td>3–14 (7.9)</td>
<td>28-week/DB, PBO-controlled</td>
<td>252</td>
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<tr>
<td>MD-01 (Van Dyck)</td>
<td>5–14 (10.1)</td>
<td>24-week/DB, PBO-controlled</td>
<td>350</td>
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<tr>
<td>MD-02 (Tariot)</td>
<td>5–14 (10.0)</td>
<td>24-week/DB, PBO-controlled in patients already receiving donepezil</td>
<td>403</td>
</tr>
<tr>
<td>MRZ-9403 (Winblad &amp; Porits)</td>
<td>&lt;10</td>
<td>12-week/DB, PBO-controlled in patients with primary dementia (AD or VaD) [10 mg/day]</td>
<td>166 Nursing home study</td>
</tr>
</tbody>
</table>
Cochrane review of memantine

Objectives
- To determine efficacy and safety of memantine for people with AD, VaD and mixed dementia

Conclusions

Moderate to severe AD:
- Pooled data indicate a beneficial effect of memantine at 6 months on cognition, activities of daily living, and behaviour
- Supported by a significant improvement in the clinical impression of change
- Patients taking memantine appeared to be less likely to develop agitation

Mild to severe dementia (AD + VaD):
- Significant benefit of memantine on global impression, cognition, function and behaviour

Tolerability:
- Memantine is well tolerated and the incidence of adverse effects is low

McShane et al. The Cochrane Library 2006
Meta-analysis on 6 studies
Cognition (ADAS-Cog/SIB), OC analysis (MMSE <20)

ADAS-Cog/SIB, week 24/28 (OC) – moderate to severe AD

SMD (fixed) 95% CI

-1 -0.5 0 0.5 1

MRZ-9605
MD-02
99679
MD-10
MD-12
MD-01
Total

p<0.00001

Favours memantine
Favours placebo

SMD=standardised mean difference;
CI=confidence interval

Winblad et al. Dement Geriatr Cogn Disord 2007; 24: 20–27
Meta-analysis on 6 studies
Global status (CIBIC-Plus), OC analysis (MMSE <20)

CIBIC-Plus, week 24/28 (OC) – moderate to severe AD

SMD (fixed) 95% CI

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SMD</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRZ-9605</td>
<td>-0.5</td>
<td>(-1,0)</td>
<td>&lt;0.0001</td>
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<tr>
<td>MD-10</td>
<td>-0.5</td>
<td>(-1,0)</td>
<td>&lt;0.0001</td>
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<tr>
<td>MD-01</td>
<td>-0.5</td>
<td>(-1,0)</td>
<td>&lt;0.0001</td>
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<td>(-1,0)</td>
<td>&lt;0.0001</td>
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<td>99679</td>
<td>-0.5</td>
<td>(-1,0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MD-12</td>
<td>-0.5</td>
<td>(-1,0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total</td>
<td>-0.5</td>
<td>(-1,0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SMD=standardised mean difference; CI=confidence interval

Winblad et al. Dement Geriatr Cogn Disord 2007; 24: 20–27
Meta-analysis on 6 studies
Function (ADCS-ADL_{23/19}), OC analysis (MMSE <20)

ADCS-ADL_{23/19}, week 24/28 (OC) – moderate to severe AD

SMD (fixed) 95% CI

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>MRZ-9605</td>
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<tr>
<td>MD-02</td>
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<tr>
<td>MD-12</td>
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<tr>
<td>Total</td>
<td>p=0.0007</td>
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</tbody>
</table>

SMD=standardised mean difference; CI=confidence interval

Winblad et al. Dement Geriatr Cogn Disord 2007; 24: 20–27
Meta-analysis on 6 studies
Behaviour (NPI), OC analysis (MMSE <20)

NPI, week 24/28 (LOCF) – moderate to severe AD

SMD (fixed) 95% CI

MD-02
MD-01
MRZ-9605
MD-10
MD-12
Lu-99679
Total

Favours memantine  Favours placebo

SMD=standardised mean difference;
CI=confidence interval

p=0.03

Winblad et al. Dement Geriatr Cogn Disord 2007; 24: 20–27
### RISULTATI DELLA REVIEW COCHRANE DEL 2006 SUL RUOLO DI MEMANTINA NELL’ALZHEIMER

<table>
<thead>
<tr>
<th>Dominio</th>
<th>Miglioramento statisticamente rilevante</th>
<th>Miglioramento clinicamente rilevante</th>
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<tbody>
<tr>
<td>Alzheimer Lieve-Moderato</td>
<td>Si</td>
<td>Limitato</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Nessuno</td>
</tr>
<tr>
<td></td>
<td>Si</td>
<td>Limitato</td>
</tr>
<tr>
<td>Alzheimer Moderato-Grave</td>
<td>Si</td>
<td>Limitato</td>
</tr>
<tr>
<td></td>
<td>Si</td>
<td>Limitato</td>
</tr>
<tr>
<td></td>
<td>Si</td>
<td>Limitato</td>
</tr>
</tbody>
</table>

**Problematiche aperte:**
- Nel complesso si nota come gli studi per grado di gravità della malattia sono poco numerosi e i pazienti inclusi non sono ben caratterizzati in termini di comorbidità o di rischi vascolari.
- Gli studi sono stati brevi e con campioni di piccole dimensioni per poter osservare qualsiasi effetto di memantina sulle aspettative di vita.
- Mancano valutazioni sulla qualità della vita dei pazienti e ricadute sui caregiver.
Pooled Analyses on Cognitive Effects of Memantine in Patients with Moderate to Severe Alzheimer’s Disease

Murat Emre, Patrizia Mecocci, and Karina Stender

- A significantly higher proportion of memantine-treated patients showed improvement on each of the three clusters at study end (Week 24/28, LOCF; and OC analyses)
- The reduction in worsening seen at Week 12 persisted for memantine-treated patients compared with those receiving placebo at Week 24/28 (LOCF)

*p<0.05; **p<0.01; ***p<0.001
Effects of memantine on cognition in patients with moderate to severe Alzheimer’s disease: post-hoc analyses of ADAS-cog and SIB total and single-item scores from six randomized, double-blind, placebo-controlled studies

Patrizia Mecocci¹*, Anna Bladström² and Karina Stender²

*\(p<0.05\); **\(p<0.01\); ***\(p<0.001\)
Efficacia di memantina sulle attività funzionali

ADCS-ADL<sub>19</sub> singoli item (LOCF), MdA da moderatamente grave a grave

Variazione media dal basale (SE)

* p<0.05; ** p<0.01

Winblad et al. Poster at ICAD 2006
Memantina migliora il grado di autonomia del paziente e riduce il carico del caregiver

- Memantina 20mg/die migliora il grado di autonomia dei pazienti con MdA di grado moderatamente severo-severo, aumentando la probabilità che rimangano autonomi per più tempo (28 sett.; Odds Ratio = 3.03; 95% CI = 1.38, 6.66)

- Memantina riduce il tempo di assistenza dei caregiver di 51,5 ore/mese
  - circa 1,5 ore al giorno

Efficacia di memantina sui sintomi comportamentali

Singoli item NPI, sett. 24/28, LOCF, (MMSE <20)

Efficacia di memantina sui sintomi comportamentali

Ritardo dell'insorgenza dei sintomi nei pazienti asintomatici al basale, sett. 24/28, LOCF (MMSE <20)

Incremento dell’utilizzo di farmaci psicotropi dopo interruzione di memantina

AC=anticonvulsivanti; AD=antidepressivi; AP=antipsicotici; ANX=ansiolitici; S/H=sedativi/ipnotici
A 24-Week Open-Label Extension Study of Memantine in Moderate to Severe Alzheimer Disease

Barry Reisberg, MD; Rachelle Doody, MD, PhD; Albrecht Stöffler, MD; Frederick Schmitt, PhD; Steven Ferris, PhD; Hans Jörg Möbius, MD, PhD

**Background:** This study is an extension of a 28-week, randomized, double-blind, placebo-controlled study of memantine in 232 patients with moderate to severe Alzheimer disease.

**Objective:** To evaluate long-term memantine treatment in moderate to severe Alzheimer disease.

**Design, Setting, and Patients:** Open-label, 24-week extension trial. Raters remained blind to the patients’ initial study treatment. Patients (n=175) were enrolled from the previous double-blind study in an outpatient setting.

**Intervention:** Twenty mg of memantine was given daily.

**Main Outcome Measures:** Efficacy assessments from the double-blind study were continued and safety parameters were monitored.

**Results:** Patients who switched to memantine treatment from their previous placebo therapy experienced a significant benefit in all main efficacy assessments (functional, global, and cognitive) relative to their mean rate of decline with placebo treatment during the double-blind period (P<.05). The completion rate for the extension phase of the study was high (78%) and the favorable adverse event profile for memantine therapy was similar to that seen in the double-blind study.

**Conclusion:** These results extend previous findings that demonstrated the efficacy and safety of memantine in the treatment of patients with moderate to severe Alzheimer disease.

Arch Neurol. 2006;63:49-54
Long-term treatment with memantine
CIBIC-Plus, mean score (OC analysis)

Reisberg et al. Arch Neurol 2006; 63: 49–54
Long-term treatment with memantine
ADCS-ADLsev, mean change (OC analysis)

Reisberg et al. Arch Neurol 2006; 63: 49–54
Long-term treatment with memantine
SIB, mean change (OC analysis)

Improvement  Worsening

-20  -15  -10  -5  0  5
SIB mean change from baseline

0  4  12  28  40  52
Week

Double-blind phase  Open-label extension

n=95  n=80  n=95  n=94  n=95  n=80  n=79  n=75  n=74  n=66  n=70
Reisberg et al. Arch Neurol 2006; 63: 49–54
Memantine augments the effects of cholinesterase inhibition in the treatment of Alzheimer’s disease

Oscar L Lopez, James T Becker, Abdus Wahed, Judith A Saxton, Robert Sweet, Dr, David Wolk, William Klunk and Steven T DeKosky


**Background:** Patients using cholinesterase inhibitors (ChEIs) have a delay in nursing home (NH) admission compared to those who were not using the medication. There are no long-term studies of the effects of memantine in combination with ChEIs use in Alzheimer’s disease (AD). This study was conducted to examine the effects of ChEIs and memantine on time to death and time to NH admission.

**Methods:** Time to NH admission and death was examined in 943 Probable AD patients who had at least a one-year follow-up evaluation. Of these patients, 140 (14.9%) used both ChEIs and memantine, 387 (45.0%) used only ChEIs, and 416 (40.1%) used neither. The mean follow-up time was 62.3 ± 35.8 months. The analysis was conducted with multivariable Cox proportional hazard models controlling for critical covariates (i.e., age, education level, gender, severity of the dementia, hypertension, diabetes mellitus, heart disease, psychiatric symptoms, and use of psychotropic medications).

**Results:** Compared to those who never used cognitive enhancers, patients who used ChEIs had a significant delay in NH admission (HR: 0.37, 95%CI: 0.27 - 0.49); this effect was significantly augmented with the addition of memantine (HR: 0.29, 95%CI: 0.11 - 0.72) (memantine+ ChEI vs. ChEI alone). ChEIs alone, or in combination with memantine had no significant association on time to death.

**Conclusions:** This observational study revealed that the addition of the NMDA receptor antagonist memantine to the treatment of AD with ChEI significantly altered the treated history of AD by extending time to nursing home admission.
Memantine augments the effects of cholinesterase inhibition in the treatment of Alzheimer’s disease

Oscar L Lopez, James T Becker, Abdus S Wahed, Judith Saxton, Robert A Sweet, Dr, David A Wolk, William Klunk and Steven T DeKosky

*J. Neurol. Neurosurg. Psychiatry* published online 8 Mar 2009;

![Graph showing the estimated proportion admitted to nursing home over follow-up time in years. The graph compares two treatments: 1. Memantine + ChEIs and 2. ChEIs alone.](image-url)
Tollerabilità

Eventi avversi osservati (frequenza > 4% con memantina) in pazienti con Malattia di Alzheimer moderatamente severa-severa durante trattamento con memantina 10-20 mg/die (n=299) o placebo (n=288) in studi multicentrici randomizzati in doppio cieco.

Tolerability: withdrawal rates from memantine studies

- Memantine’s overall withdrawal rate was comparable to the placebo rate

<table>
<thead>
<tr>
<th></th>
<th>Memantine n (%)</th>
<th>Placebo n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated</td>
<td>1,784</td>
<td>1,595</td>
<td>3,379</td>
</tr>
<tr>
<td>Patients completed</td>
<td>1,465 (82.1)</td>
<td>1,281 (80.3)</td>
<td>2,746 (81.3)</td>
</tr>
<tr>
<td>Patients withdrawn</td>
<td>319 (17.9)</td>
<td>314 (19.7)</td>
<td>633 (18.7)</td>
</tr>
</tbody>
</table>

H. Lundbeck A/S, Data on file
Memantine Treatment in Patients With Moderate to Severe Alzheimer Disease Already Receiving Donepezil A Randomized Controlled Trial
Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I.; for the Memantine Study Group

SIB and ADCS-ADL19 by Visit (Observed Case) and at End Point (LOCF)
Memantine Treatment in Patients with Mild to Moderate Alzheimer’s Disease Already Receiving a Cholinesterase Inhibitor: A Randomized, Double-Blind, Placebo-Controlled Trial

Anton P. Porsteinsson1,*, George T. Grossberg2, Jacobo Mintzer3 and Jason T. Olin4†, for the Memantine MEM-MD-12 Study Group

1Alzheimer’s Disease Care, Research and Education Program, University of Rochester, School of Medicine and Dentistry, Rochester, NY, USA; 2St. Louis University, St. Louis, MO, USA; 3Medical University of South Carolina, Charleston, SC, USA; 4Forest Research Institute, Jersey City, NJ, USA

Abstract: Objective: To evaluate the efficacy and safety of memantine in patients with mild to moderate Alzheimer’s disease (AD) receiving cholinesterase inhibitor (ChEI) treatment. Methods: Participants (N= 433) with probable AD, Mini-Mental State Exam (MMSE) scores between 10-22 (inclusive), and concurrent stable use of ChEIs (donepezil, rivastigmine, galantamine) were randomized to placebo or memantine (20 mg once daily) for 24 weeks. Primary outcomes were changes from baseline on the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) and on Clinician’s Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) score. Secondary measures comprised the 23-item Alzheimer Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL23), Neuropsychiatric Inventory (NPI), and MMSE. Results: At the end of the trial, there were no statistically significant differences between the memantine- and placebo group on primary and secondary outcome measures. The incidence of adverse events (AEs) was similar between the two groups, with no AE occurring in more than 5% of memantine-treated patients and at a rate twice that of the placebo group. Conclusions: In this trial, memantine did not show an advantage over placebo based on protocol-specified primary or secondary analyses in patients with mild to moderate AD on stable ChEI regimens. There were no significant differences in tolerability and safety between the memantine- and placebo groups.
Long-term Course and Effectiveness of Combination Therapy in Alzheimer Disease

Alireza Atri, MD, PhD,* Lynn W. Shaughnessy, BS,*† Joseph J. Locascio, PhD,* and John H. Growdon MD*

Objective: To compare the real-world clinical effectiveness and long-term clinical trajectory in patients with Alzheimer disease (AD) treated with combination (COMBO) therapy consisting of cholinesterase-inhibitor (CI) plus memantine (MEM) versus CI alone versus no treatment with either.

Methods: Three hundred eighty-two subjects with probable AD underwent serial clinical evaluations at a memory disorders unit. Cognition was assessed by the Information-Memory-Concentration subscale of the Blessed Dementia Scale (BDS) and function was assessed by the Weintraub Activities of Daily Living Scale (ADL) at 6-month intervals. One hundred forty-four subjects received standard care without CI or MEM (NO-RX), 122 received CI monotherapy, and 116 received COMBO therapy with CI plus MEM. Mean follow-up was 30 months (4.1 visits) and mean cumulative medication treatment time was 22.5 months. Rates of decline were analyzed using mixed-effects regression models, and Cohen’s $d$ effect sizes were calculated annually for years 1 to 4.

Results: Covarying for baseline scores, age, education, and duration of illness, the COMBO group had significantly lower mean annualized rates of deterioration in BDS and ADL scores compared with the CI ($P < 0.001$; Cohen’s $d_{BDS} = 0.10 – 0.34$ and $d_{ADL} = 0.23 – 0.46$ at 1 to 2 yr) and NO-RX groups ($P < 0.001$; Cohen’s $d_{BDS} = 0.56 – 0.73$ and $d_{ADL} = 0.32 – 0.48$ at 1 to 2 yr). For the COMBO group, Cohen’s $d$ effect sizes increased with treatment duration. Similar comparisons significantly favored the CI over the NO-RX group on the BDS.

Conclusions: COMBO therapy slows cognitive and functional decline in AD compared with CI monotherapy and no treatment. These benefits had small-to-medium effect sizes that increased with time on treatment and were sustained for years.

Key Words: treatment efficacy, modeling progression, cholinesterase inhibitor, memantine, memory, cognition and function in dementia

### Prescrizione

**Gazzetta Ufficiale n. 65 del 19 Marzo 2009**

**Nota 85**

**Donepezil - Galantamina - Rivastigmina - Memantina**

<table>
<thead>
<tr>
<th>Inibitori dell'acetylcolinesterasi:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- donepezil</td>
</tr>
<tr>
<td>- galantamina</td>
</tr>
<tr>
<td>- rivastigmina</td>
</tr>
<tr>
<td>- memantina</td>
</tr>
</tbody>
</table>

La prescrizione a carico del SSN, su diagnosi e piano terapeutico delle Unità di Valutazione Alzheimer (UVA) individuate dalle Regioni e dalle Province Autonome di Trento e Bolzano, è limitata ai pazienti con malattia di Alzheimer di grado lieve, con MMSE tra 21 e 26 (donepezil, rivastigmina, galantamina) o moderato, con MMSE tra 10 e 20 (donepezil, rivastigmina, galantamina, memantina).

Alla UVA è affidato il compito di effettuare o, eventualmente, confermare una diagnosi precedente e di stabilire il grado di severità in accordo alla scala MMSE.

Il piano terapeutico deve essere formulato sulla base della diagnosi iniziale di probabile demenza di Alzheimer di grado lieve-moderato.

La risposta clinica dovrà essere monitorata ad intervalli regolari dall'inizio della terapia:

- a 1 mese, per la valutazione degli effetti collaterali e per l'aggiornamento del piano terapeutico;
- a 3 mesi, per una prima valutazione della risposta e per il monitoraggio della tollerabilità; la rimborsabilità del trattamento oltre i tre mesi deve basarsi sul non peggioramento dello stato cognitivo del paziente valutato tramite MMSE ed esame clinico;
- ogni 6 mesi per successive valutazioni della risposta e della tollerabilità.
**Il Münchhausen-Trilemma**, chiamato anche **trilemma di Agrippa**, è un termine coniato dal filosofo Hans Albert per definire l'impossibilità di provare alcuna verità assolutamente certa. È definito trilemma perché pone tre possibilità, di cui nessuna riesce a soddisfare l'assoluta certezza necessaria a fondare una conoscenza, ed il suo nome proviene ironicamente dal Barone di Münchhausen, che si dice sia riuscito a tirarsi fuori da una poza di fango tirandosi per i capelli. Albert pose il problema in questi termini:

Ogni affermazione, per essere assolutamente certa, deve essere giustificata, ma a loro volta queste giustificazioni devono essere giustificate. Questo processo, tuttavia, non ha fine dato che ogni giustificazione dovrebbe essere giustificata, arrivando ad una situazione per cui le giustificazioni dovrebbero moltiplicarsi all'infinito;

Esiste un principio autoevidente, o accettato dal senso comune, o ritenuto vero per il principio di autorità. In questo caso, però, l'intenzione di fondare una conoscenza assolutamente certa viene a crollare e si cade nel dogmatismo

Qualsiasi affermazione viene provata tramite un'argomentazione circolare e, quindi, errata.
CONFRONTO DEI COSTI PER I PRIMI 12 MESI DI TERAPIA

* sono state considerate le DDD (Defined Daily Dose)
è la prima volta che il SSN, con una nota limitativa,
rimborsa una condizione meno severa (forma moderata) ed esclude dalla rimborsabilità la condizione più severa (forma grave). Tutti gli altri esempi delle note limitative vanno nella direzione opposta, come la nota 13, la nota 48, la nota 66, la nota 79 (rimborsabilità per livelli di rischio o di malattia più accentuati).
Come spiegheranno i medici delle UVA ai familiari dei pazienti il fatto che all’aggravarsi delle condizioni cliniche del loro congiunto il farmaco diventa a pagamento?