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Memantine (brand name: Memary)

An NMDA antagonist, memantine may induce neurotoxicity

Cochrane team criticises ECDC's draft advice on oseltamivir use

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"Talk about harm, not risk"

Translated from the editorial in Med Check-TIP (in Japanese) Mar. 2016 ; 16 (64):30

On February 21st, Dr. Andrew Herxheimer died, aged 90 years. In 1962, he launched the Drug and Therapeutic Bulletin (DTB) in Britain, an independent drug bulleting which receives no support from pharmaceutical companies. He left behind great achievements in establishing and promoting the International Society of Drug Bulletins (ISDB), of which the Med Check TIP is a member. The principal role of independent drug bulletins is **"promoting rational use of medicines"** which has led to today's "evidence based medicine". In the Cochrane Collaboration, he led discussion on conditions for maintaining independence from pharmaceutical companies, and also was an opinion leader in discussing harms.

Dr. Andrew Herxheimer said frequently **"Talk about harm, not risk"** when he discussed on benefits and harms of medicines. These words impressed me the most. He explained "Very often people use the word **risk** when they mean **harm**, and this causes ambiguities and confusion." He proposed four dimensions for both benefits and harms as follows:

1. Its **nature**, described by its quality, its intensity, and its time course (onset, duration and reversibility).
2. The **probability** that it will occur.
3. Its **importance to the person experiencing it**.
4. How the benefit can be maximised or the harm **prevented** or **minimised**.

"Risk" is a "probability of harm" and only one of the aspects of harms. His idea is referred in the Chapter 8 of the ISDB manual (http://www.isdbweb.org/documents/uploads/manual_full_text.pdf).

Andrew was a man of humor as well. More than 20 years ago, during the ISDB summer school and general meeting in Japan, we came to talk about "karaoke" (orchestral music without song). When I explained that "kara" means "empty" in English, he pointed at his bald head and asked me "How do you call this in Japanese?" I answered him "atama". Then pointing at his head, he said "kara-atama" and grinned mischievously.

Dr. Herxheimer has been respected by many people. He was still clearheaded, and working actively until he passed away unexpectedly. In a way, it might have been an ideal departure.

We pray his soul may rest in peace.

In this issue, we featured a new indication "male pattern baldness" of "dutasteride", 5- α -reductase inhibitor. We have fundamental questions after reviewing it. Based on the package insert, it is indicated for "androgenic alopecia". However, is "male pattern baldness" really a disease? Does it really need to be treated?

TAMIYA, Jiro, an actor who committed suicide at the age of 43, was distressed about his sparse hair. Reportedly, he underwent hair implantation every year in Britain, and suffered from its severe complications such as migraine and memory impairment. In those days, another actor advertised wigs on TV and immediately lost his job offers. However, nowadays advertising hair tonics or wigs does not seem to affect actors' popularity. Male-pattern baldness is also a proof of high sexual function in males.

Is alopecia (sparse hair) a "disease" which is more serious than harms such as sexual impairment, cognitive impairment, depression, suicide, and high-grade prostate cancer induced by dutasteride?

Doctors and pharmacists should provide appropriate information to persons who are distressed about "hair loss" to help them make a right decision and protect them from more serious harms.

Once again, we should think deeply about the words of Dr. Herxheimer: **"Talk about harm, not risk"** reminding his head and thought.

New Products

Memantine (brand name: Memary):
No value for dementia

An NMDA antagonist, memantine may induce neurotoxicity
Too many withdrawn cases due to adverse reactions

Translated from Med Check-TIP (in Japanese) Mar. 2016 : 16 (63):3-7

Abstract

●Memantine (brand name: Memary), which was launched in 2011, increases dopamine and acetylcholine like an antiparkinsonism agent, amantadine.

●Based on the result from an animal experiment, the manufacturer claims that memantine has neuroprotective property. However, memantine causes neuronal necrosis in the cingulate cortex, which is involved in cognition and emotion, at the dose close to the human clinical dose. It also induces neurotoxicity at the dose which is claimed to improve cognitive abilities. Donepezil (brand name: Aricept), which is often used in combination with memantine, potentiates this neurotoxicity.

●In patients with moderate to severe dementia, memantine used for 24 weeks is reported to have improved their symptoms. However, it was confirmed ineffective in an important endpoint. In a follow-up study conducted after the clinical trial, a half of the patients who were on the medication discontinued the treatment within 2 years. Adverse event was the reason for the discontinuation in about a half of the cases. Despite the manufacturer's claim, long-term efficacy and safety have not been established.

Delirium is a symptom. Dementia is a disease.

Dementia is a syndrome – usually of a chronic or progressive nature – in which there is deterioration in cognitive function (i.e. the ability to process thought) beyond what might be expected from normal ageing. It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, judgement and the ability to perform everyday activities. Consciousness is not affected [1]. Dementia is characterized by "a condition in which cognitive function which once developed normally deteriorate persistently because of acquired brain disease, affecting the patients' daily and social lives. It is observed when consciousness is preserved" (definition by the Japanese Society of Neurology Guideline (2010) [2]).

[1] WHO: Media centre Dementia, Fact sheet No362 (March 2015) http://www.who.int/mediacentre/factsheets/fs362/en/

To complement the definition above, "because of acquired brain disease" and "persistently" are very important factors in distinguish it from delirium, which is characterized by transient cognitive impairment [1-7].

Both dementia and delirium cause impairment in cognition and memory, and disturb judgement and behavior which are necessary for social life. Among different types of memory, both disrupt short-term memory in particular, and thus the patients forget instantly what they heard just a while ago. When they worsen, they lead to delusion and hallucination. These are common to both delirium and dementia [1-7]. Nevertheless, it should be emphasized again that delirium is a transient symptom while dementia is a disease of persistent and progressive nature that accompanies "acquired brain diseases"

Medicines for dementia

In Japan, as many as 38 kinds of anti-dementia agents, named as "cerebral circulation improving agents" or "cerebral metabolism improving agents", had been approved for treatment of dementia in the past [8-10]. Between 1998 and 1999, most of them were taken off the market. None of the medicines approved in or before 1998 still hold a clear indication for treatment of dementia today.

Currently, only 4 medicines are indicated for treatment of dementia like in other countries; namely donepezil (brand name: Aricept etc.); cholinesterase inhibitors, galantamine

Table ：Approved products for dementia（as of March, 2016）

Generic name	Brand name	Pharmacology	Launch date	Indications *a
donepezil	Aricept	Inhibition of cholinesterase (cholinergic agonists)	November, 1999	No restriction by severity *b
	Generic products		November, 2011	
galantamine	Reminyl		March, 2011	Mild-moderate
rivastigmine	Rivastouch patch, Exelon patch		July, 2011	Mild-moderate
memantine	Memary	Inhibition of NMDA-R (increase of dopamine and acetylcholine)	June, 2011	Moderate & severe

*a: All are indicated for "suppressing the progress of dementia symptoms in dementia of the Alzheimer's type". It is important to note that these indications do not mean "controlling the progress of dementia itself", but "transiently suppressing the dementia symptoms." All the medicines, except for donepezil, have restriction by severity in Japan.
*b：Among the donepezil preparations, Aricept was approved for treating Lewy body dementia in September 2014 in Japan.
NMDA-R: NMDA receptor

(Reminyl) and rivastigmine (Rivastouch, Exelon Patch); and an NMDA receptor antagonist (NMDA antagonist), memantine (Memary) (**Table**).

Cholinesterase inhibitors are expected to activate mental activities by increasing acetylcholine in the brain. Memantine is expected to exhibit the similar effect by inhibiting NMDA receptors which glutamate acts on, and paradoxically increasing dopamine and acetylcholine.

Expectation for memantine

When the brain is acutely damaged by cerebral infarction or trauma, glutamate accumulates around NMDA receptors in the damaged brain tissue, inducing excitotoxicity in the brain. In such a condition, NMDA antagonists are reported to prevent glutamate from accumulating in the receptors and protect the nerves [11]. Reasoning from this line of evidence, it has been hypothesized that glutamate, by chronic low-grade overstimulation of NMDA receptors, may contribute to the neuropathology of Alzheimer's disease (AD), and that drugs that block NMDA receptors might be neuroprotective in AD [12].

An NMDA antagonist, memantine induces neurotoxicity.

On the other hand, memantine induces neurotoxicity. According to the information submitted for approval of memantine [11], the medicine protected against neuronopathy in rats at 1.7 mg/kg and 3.3 mg/kg in human equivalent dose (HED: Note 1, [13]). Meanwhile, HED of non-observed effect level (NOEL) in rats is 0.17-0.25 mg/kg, and is lower than the human clinical dose（0.4 mg/kg= 20 mg/50 kg. Furthermore, HED of 25 mg/kg, the dose at which necrosis was caused in the retrosplenial cortex and cingulate cortex, was 4 mg/kg. HED (2 mg/kg) of NOEL, at which no necrosis was observed, was only 5 times higher than the clinical dose (0.4 mg/kg.) This indicates that the dose that demonstrates protective effect (1.7-3.3 mg/kg) and the dose that causes toxicity (4 mg/kg) are almost the same. The manufacture explains the pathogenic mechanism as follows [11].

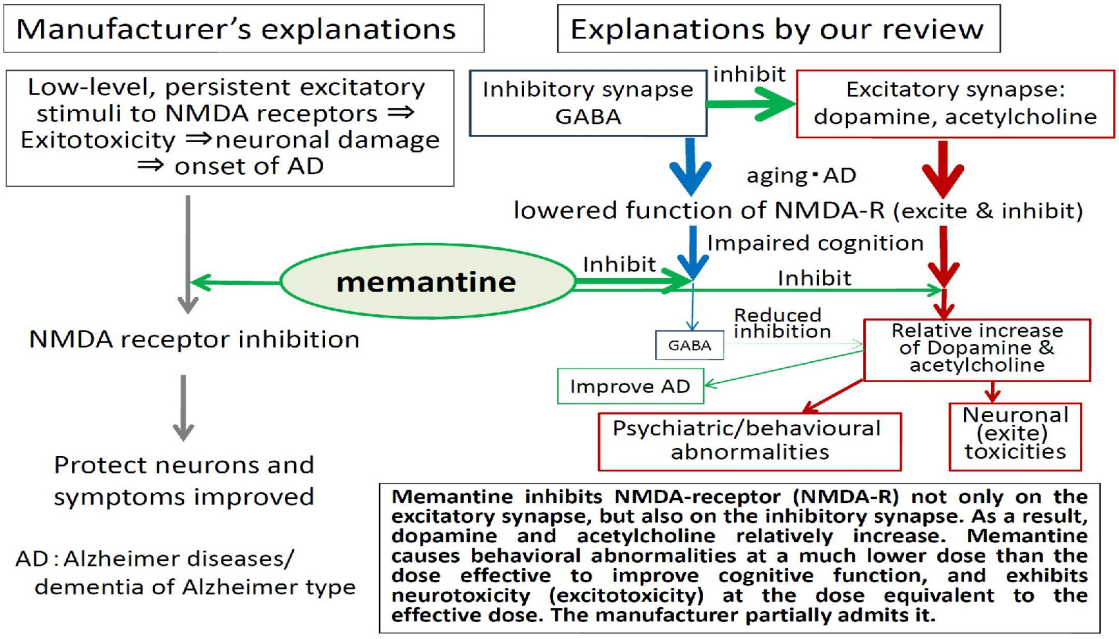
The Cingulate cortex neurons have Ach (acetylcholine) receptors, muscarinic receptors, and the release of Ach around the receptors is regulated by GABAergic neurons. On GABA neurons, NMDA receptors are present. When NMDA receptor channel antagonists suppress the NMDA receptors on the GABAergic neurons, GABA can no longer regulate the release of Ach. Therefore, by administrating memantine, the NMDA receptors on GABAergic neurons are suppressed, causing the persistent release of Ach. The excessive Ach is believed to induce histological damage in the cingulate cortex neurons.

This explanation clearly states that while NMDA antagonists protect the nerves, they also damage the nerves. However, it is inadequate because it misses out another important point. When the NMDA receptors on the GABAergic neurons are suppressed, it leads to the excess of not only Ach, but also dopamine, inducing even more intense excitotoxicity to the neurons [12, 14] (**Figure 1**). At the effective dose sufficient to improve cognitive abilities, memantine exhibited mild neurotoxicity [12, 14]. When it was combined with donepezil, the toxicity was potentiated [12]. Therefore, the protective effect on nerves which the manufacturer claims is questionable. The cingulate gyrus, where memantine causes necrosis, plays an important role in emotion, learning, and memory [15]. In addition, NMDA antagonists cause memory and behavioral impairment at a much lower dose than the dose which exhibits the protective effect [12, 14].

Decreased function of NMDA receptors is deeply related to the onset of schizophrenia [16-18] and also is an underlying factor of pathogenesis of Alzheimer's disease. NMDA antagonists deteriorate the decreased function of NMDA receptors even further, lowering the function of inhibitory neurons. This activates excitatory neurons and induces excitotoxicity [12, 13, 16].

Figure 1 shows the explanation about the pathogenic mechanism of Alzheimer's disease and the effects of memantine by the manufacturer as well as that by the Med Check TIP.

Figure 1：Pathogenesis of dementia（AD）and action of memantine

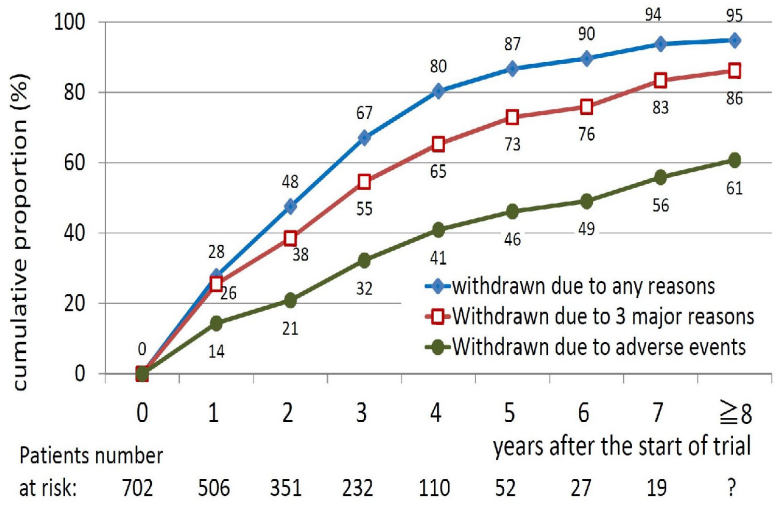


Clinical efficacy is confirmed only up to week 24

In a double-blind randomized controlled trial (RCT), memantine 20 mg or placebo were given to 432 patients with moderate to severe dementia of the Alzheimer's type (Note 2) for 24 weeks. In the memantine group, the dose was increased weekly by 5 mg increments from 5 mg/day to 10 mg/day and 15 mg/day in the first 3 weeks followed by 20 mg/day for 21 weeks (total 24 weeks).

The difference in change in score on the SIB-J (Note 3), which is designed to evaluate cognitive function in severer dementia, between the two groups (primary outcome: at 24 weeks) was 4.53 points and significant (p=0.0001). In the final evaluation, the significant difference was also confirmed (p<0.0001) [11]. In another double-blind controlled trial, although the evaluation of cognitive function significantly improved on the SIB-J, a dose-response was not observed on the ADCS ADL-J (Note 3) in the primary outcome (change in score at 24 weeks: comparing before and after the treatment). The ADCS ADL-J evaluates activities of daily living which are more important in a real life. The result of a parallel-group comparison showed no significant difference between the placebo and memantine 20 mg/day groups (sample size: 260, p=0.8975) [11]. The parallel-group comparison which was conducted as the secondarily analysis should have been a primary analysis.

Figure 2： Cumulative proportion (%) of withdrawn after memantine use



Three major reasons: adverse events, poor compliance, consent withdrawn.

All reasons other than three major reasons, the followings were reported: no need of treatment, inadequate alternatives/monitoring, did not visit, contravene exclusion criteria, difficult to visit, institutionalization, and others

Editor's note 1：Because it is hard to believe that dementia was relieved, it is strange that medication was considered to be unnecessary. It could be either the patients originally did not need the medication or they switched to other medicines. Details are unknown.

Editor's note 2：It is not clear what "inadequate alternative/monitoring" means.

In a long-term follow-up, a half of the patients withdrew within 2 years

Another study [17] was conducted to follow-up 702 participants involved in a randomized controlled trial for moderate to severe dementia of the Alzheimer's type for a long time (memantine was used for average 798.1 days, maximum 3,373 days) after the trial (RCT). The study reported as follows:

Incidence of adverse events was 71.0% to 88.9%, and incidence of side effects was 5.6% to 32.1% by every 52-week period and there was no association observed between the incidences and duration of use nor between long-term use and particular side effects. The main reason for discontinuation was "adverse events." Many cases of adverse events and discontinuation were reported, which occurred because of changes in environment of home care and institutionalization as a result of the progress of an underlying disease. The MMSE scores gradually declined. The study suggested that no problem in tolerability was identified in a long-term use of memantine and that it can inhibit the deterioration of cognitive function in a long-term.

We review the relevance of this interpretation. **Figure 2** indicates the cumulative proportion (Note 4) of discontinuation by the reasons of discontinuation. The figure was reconstructed based on the data from the reference 17.

The conclusion of the study, "there is no problem in tolerability", is based on that the proportions of adverse events that led to discontinuation were 12 % in the first year, and 4.3% to 11% in the subsequent years, and did not increase. However, in the cumulative proportion, 48% of the patients discontinued for some reason, and in about a half of the cases, adverse events were involved. This clearly shows that there was a problem in tolerability.

Symptoms were likely to improve in patients who continued the treatment for a long-term

The study report the data as if memantine protected the rapid progression of the disease by comparing the results from the CERAD study which was conducted in the U.S. before donepezil and memantine were introduced. In the CERAD study, the MMSE scores rapidly declined from 10 points before the treatment to 1.6 points at 2 years. On the other hand, the data in this study showed that the MMSE scores before the treatment was 9.7 points and it declined to 6.3 points at 2 years, 3.4 points at 5 years, and 2.9 points at 7 years.

However, the number of patients followed decreased substantially from 702 in the beginning to 351 at 2 years, 52 at 5 years, and only 19 at 7 years. Because longer the duration, more patients discontinued the treatment due to "institutionalization", patients who discontinued had severer symptoms with more complications while patients who continued were healthier with relatively milder symptoms and less complications. The effect of withdrawal of severer patients, not the effect of memantine, obviously contributed to the slower decline of the MMSE scores.

Conclusion：Memantine should not be used in patients with dementia of the Alzheimer's type at any stage.

Note 1：**HED (human equivalent dose)** is a human dose converted by body surface area [13]. For example, in mice, rats, and dogs, 1/12, 1/6 and 1/2 of the dose per body weight are the HED, respectively. If "No Observed Adverse Effect Level" (NOAEL) in mice is 120 mg/kg, HED = 10 mg/kg.
Note 2：**Moderate to severe dementia** were defined as those with score ≧ 5 and ≦ 14 by MMSE (Mini Mental State Examination)[18] and with stage ≧ 6a and ≦ 7a by FAST (Functional Assessment Staging) among the assessment tools to evaluate the severity of dementia symptoms.
Note 3：**SIB-J** stands for "severe impairment battery-Japan" [19] and ADCS ADL-J for "Alzheimer Disease Cooperative Study-Activities of Daily Living inventory-Japan" [20]
Note 4：**Cumulative proportion** is not the proportion of patients who discontinued each year among the patients at risk in each year, but the cumulative proportion of patients who discontinued since the beginning of the study until the end of each year.

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Dutasteride (Zagallo®) for Androgenetic Alopecia:

Good in theory, too harmful in practice: cancer, sexual dysfunctions, suicide

Synopsis from Japanese edition of MED-CHECK TIP (No64)

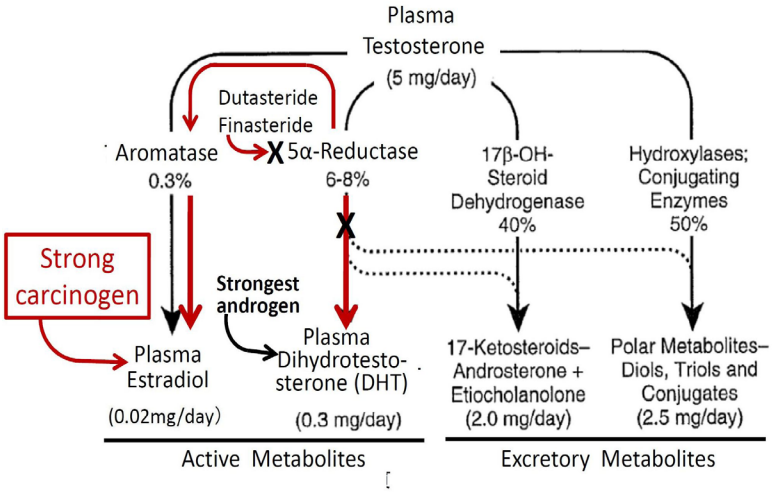
Synopsis

● Dutasteride, an ingredient of Zagallo which is newly approved in Sept 2015 for androgenetic alopecia, has been already approved and on the market for prostatic hyperplasia (Avolve®).

● It is an inhibitor of 5- α reductase which converts testosterone into the strongest androgen, dihydrotestosterone (DHT). It also increases estradiol which is the strongest estrogen and is one of the strongest carcinogens. (Figure 1)

● Treatment for androgenic alopecia may continue for a long term. Because the maximal daily dose for alopecia is the same as that for prostatic hyperplasia, the same harm with similar risk ratio can occur as used in prostatic hyperplasia. Abstract of an article on dutasteride for prostatic hyperplasia [ref 8] is shown in the Box1.

Figure 1 : Metabolism of testosterone, 5 α -reductase and its inhibitors



Modified From Wilson et al ed. Williams Textbook of Endocrinology 9th ed 1998 [7].
Editorial notes: If 5α-reductase is inhibited, testosterone may be converted more through other pathways, such as via aromatase to estradiol which is one of the strongest carcinogens to induce high malignancy grade prostatic cancer.

Box 1. Abstract of an article on dutasteride for prostatic hyperplasia (ref [8])

●Dutasteride and finasteride reduced the volume of prostate and improved symptoms of dysuria (difficulties in micturition) but increased loss of libido, erectile and ejaculation dysfunction and gynecomastia.

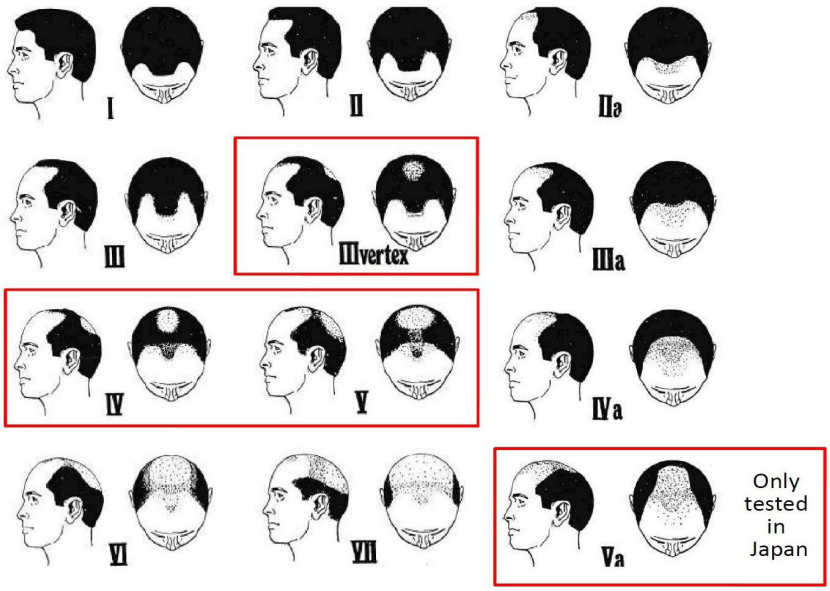
●Especially it is problematic that it increased high malignancy grade prostatic cancer (grade 8 - 10) increased compared with placebo group in the randomized controlled trial (RCT) of dutasteride for prostatic hyperplasia: **14** patients in the dutasteride group (N=2442) after 3 to 4 years, while **0** in the placebo group (N=2338): **odds ratio 28.52**: 95%CI: 3.44- ∞, p=0.0001). This fact is not described in the package insert of products of dutasteride (both Avolve® and Zagallo®).

●In the RCT of finasteride, high grade (8 -10) prostatic cancer occurred 2.0 % (95/4775) in finasteride group compared with 1.2 % (60/5123) in the placebo group: Risk ratio was 1.70 (95%CI : 1.23-2.34, p=0.001).

●The proportion of patients who were diagnosed as having prostatic cancer was lower in the dutasteride or finasteride group than the placebo group. However this was because proportion of biopsied patients was lower due to decreased PSA level by these agents.

● Norwood-Hamilton classification for androgenic alopecia and the types which were tested in the randomized controlled trial of dutasteride are shown in Figure 2.

Figure2: Norwood-Hamilton classification for androgenic alopecia and the types which were tested in the randomized controlled trial of dutasteride



● Hair number at alopecic area increases by about 10 % (Table 1), but only 0.5 point out of 7 points increases on the satisfaction assessment scale (Table 2).

Table1 : Increment of number of hair in the pivotal RCT of Zagallo

Outcome measure	Duration of treatment(w)	Placebo	Zagallo 0.1mg	Zagallo 0.5mg	Propecia 1.0mg
N		181	188	184	179
(Japansese)		40	40	40	40
age 20 -50(median)		40	40	39	39
number of hairs within a circle with 2.54cm of diameter	baseline	761	721	768	764
	12W	757	781	854	815
	24W	756	784	862	820
number increased	12W	-4.0	59.6	86.4	50.9
	24W	-4.9	63.0	94.4	56.5
(Japanese)	24W	-17.3	39.4	68.5	21.3
increment (%)	12W	-0.5	8.3	11.3	6.7
	24W	-0.6	8.7	12.3	7.4
(Japanese)*b	24W	-2.3	5.5	8.9	2.8

*a: Pivotal randomized controlled trial (RCT) of Zagallo = study ARI114263
*b: baseline numbers of hairs of the Japanese population were not reported. Hence increments (%) for the Japanese population were shown by comparing with the average baseline of total population. This may be one of the reasons why increments (%) in the Japanese population were low in all groups.

Table2 : Self assessment of satisfaction in the pivotal RCT *a of dutasteride (Zagallo)

Outcome measure	Participants	Duration of treatment (w)	Placebo	Zagallo 0.02mg	Zagallo 0.1mg	Zagallo 0.5mg	Propecia 1.0mg
Hair growth Index (HGI) average *b	All	12W	1.1	1.1	2.8	3.2	2.5
		difference to PL		0.1	1.8	2.2	1.4
		P value		0.8	<0.001	<0.001	<0.001
	only Japanese	12W	-0.6	-0.1	2.6	2.8	2.0
		difference to PL		0.6	3.2	3.4	2.7
		P value		0.41	<0.001	<0.001	<0.001
Hair growth satisfaction scale (HGSS) average *c	All	12W	9.1	8.5	11.4	12.0	10.4
		difference to PL		-0.7	2.3	2.8	1.3
		P value		0.4	0.002	<0.001	0.084
	only Japanese	12W	5.9	3.6	7.2	9.2	7.1
		difference to PL		-2.3	1.3	3.3	1.2
		P value		0.12	0.39	0.024	0.41

*a: Pivotal RCT (study ARI114263)
*b: HGI: -3～+3 for 4 items: maximum point is +12. average is calculated by least square mean. Hence +2.2 means +0.55 for individual item (among 7 points): it means between 0 (not changed) and 1 (slight increae).
*c: HGSS: -3～+3 for 5 items: maximum point is +15. average is calculated by least square mean. Hence +2.8 means +0.58 for individual item (among 7 points): it means between 0 (Neither is applicable) and 1 (slightly satisfied)

Table 3: Common adverse reactions to dutasteride in REDUCE trial or adverse events leading to discontinuation of study agents

Adverse reactions	Placebo N=4126		Dutasteride N=4105		Odds Ratio (OR)		P value Fisher's Exact test	NNTH
	n	(%)	n	(%)	OR	95% CI		
Any	604	14.6	904	22.0	1.65	1.47– 1.84	< 0.0001	14
Erectile dysfunction	237	5.7	369	9.0	1.62	1.37– 1.92	< 0.0001	31
Gynecomastia	43	1.0	76	1.9	1.79	1.23– 2.61	0.0022	124
Semen volume decreased	9	0.2	56	1.4	6.33	3.13– 12.8	< 0.0001	87
Libido decreased	65	1.6	137	3.3	2.16	1.60– 2.91	< 0.0001	57
Loss of libido	54	1.3	79	1.9	1.48	1.04– 2.10	0.0288	162
Nervous system disorders	34	0.8	49	1.2	1.45	0.92– 2.33	0.093	na
Adverse events leading to permanent discontinuation of study agent								
Any	244	5.9	342	8.3	1.45	1.22– 1.72	< 0.0001	41
Erectile dysfunction	36	0.9	97	2.4	2.75	1.85– 4.16	< 0.0001	67
Gynecomastia	2	0.0	15	0.4	7.56	1.76– 68.2	0.0015	316
Semen volume decreased	1	0.0	8	0.2	8.05	1.08– 357	0.0192	586
Psychiatric disorders	29	0.7	58	1.4	2.02	1.27– 3.29	0.0016	141
Libido decreased	10	0.2	27	0.7	2.73	1.28– 6.32	0.0049	241
Loss of libido	11	0.3	16	0.4	1.46	0.64– 3.49	0.3285	na
Depression	3	0.1	6	0.1	2.01	0.43– 12.4	0.3134	na

N: safety population (ITT population), na: not assessed
These are calculated by editorial team based on the data from ref [27].
Treatment with 0.5mg of dutasteride in androgenic alopecia for 4 years may induce these adverse reactions by the similar odds ratios.

● On the other hand, harm such as loss of libido, erectile dysfunction, ejaculation disorder, decreased semen volume and gynecomastia due to decreased male function may occur based on the adverse reactions reported in the randomized controlled trial (RCT) of dutasteride for prostatic hyperplasia (REDUCE trial) (Table 3).

● In the REDUCE trial (Figure 3, Figure 4), 8241 patients with prostatic hyperplasia were assigned to dutasteride or placebo group (Table 4).

Figure 3: Study Design of REDUCE Trial and Biopsy [ref 15]

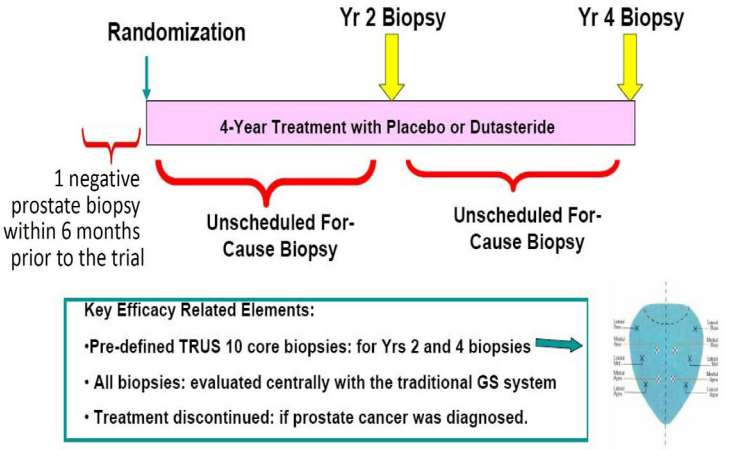


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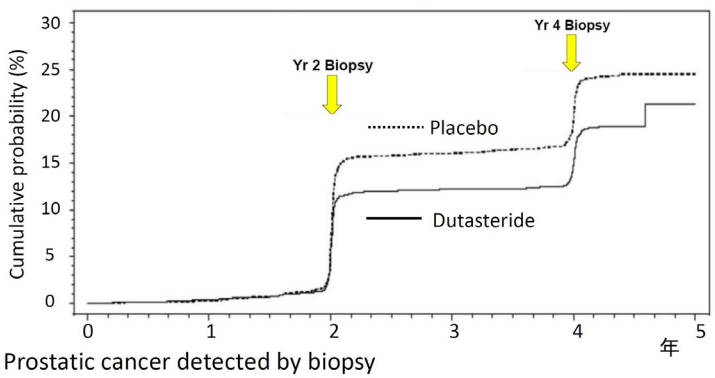
Figure 4: Cumulative probability of prostatic cancer in REDUCE trial



Prostatic cancer detected by biopsy

Placebo	11	244	592	718	858
Dutasteride	15	209	444	535	659

At the first year (before scheduled biopsy), more prostatic cancers were detected in dutasteride group than placebo group (15 vs 11). However, more were detected in placebo group after the scheduled Yr 2 biopsy. Difference did not increase after Yr4 biopsy.

● Among the biopsy population (N_3 or N_4), prostatic cancer of any grade of Gleason score (GS) were significantly less detected in dutasteride group than placebo group. However, prostatic cancer with high grade of malignancy (especially of modified GS 8 -10) were significantly more detected in the dutasteride group than placebo group (Table 4).

Note that 14 patients had high grade of malignant prostate cancer (modified GS: 8-10) in the dutasteride group after 3 to 4 years, while 0 in the placebo group: odds ratio 28, p=0.0001) (Table 5). This fact is not described in the package insert of products of dutasteride (both Avolve® and Zagallo®) in Japan.

Table 4 : Prostatic cancer detected by Gleason score after treatment of prostatic hyperplasia with dutasteride for 4-years

population (N) / Gleason-score		All period PL n	PL %	D n	D %	Odds Ratio (OR) OR	95%CI	p value *e
ITT-population(N_0)		4126		4105		(HR)		
GS*a 2-10		871	21.1	669	16.3	0.77	0.70-0.84	<0.0001
Efficacy population (N_1)		4073		4049				
Biopsied at least once (N_2)		3424	84.1	3305	81.6	0.84	0.75-0.95	0.0036
Biopsy population(N_3) *b		3407		3299				
GS*a 2-10		850	24.9	657	19.9	0.75	0.67-0.84	<0.0001
GS*a 8-10		19	0.6	29	0.9	1.58	0.89-2.83	0.1469
Biopsy population (N_4)		3388		3284				
Reanalysis by modified Gleason score (M-GS) *c	M-GS 0	2557	75.5	2643	80.5	1.34	1.19-1.51	<0.0001
	M-GS 2-4	0	0.0	0	0.0			
	M-GS 5-6 *d	604	17.8	434	13.2	0.70	0.61-0.80	<0.0001
	M-GS 7	211	6.2	175	5.3	0.85	0.69-1.04	0.128
	M-GS 8-10	16	0.5	32	1.0	2.07	1.14-3.79	0.020

*a : Original analysis by Gleason score(GS)。GS 2-10 means prostatic cancer among which cancer with GS 2-4 was not reported in both groups.
*b : Data from ref [16]. All other data are from ref [15].
*c: Reanalysis was performed by modified Gleason score. A few biopsy slides were not available for the reassessment by modified Gleaso score. Hence there are some difference in N_3 and N_4.
*d : Difference in the detection of low grade prostatic cancer may be due to proportion biopsied according to the difference in PSA value between both groups.
*e : P value vs placebo is based on Fisher's exact test. P values not adjusted for multiplicity

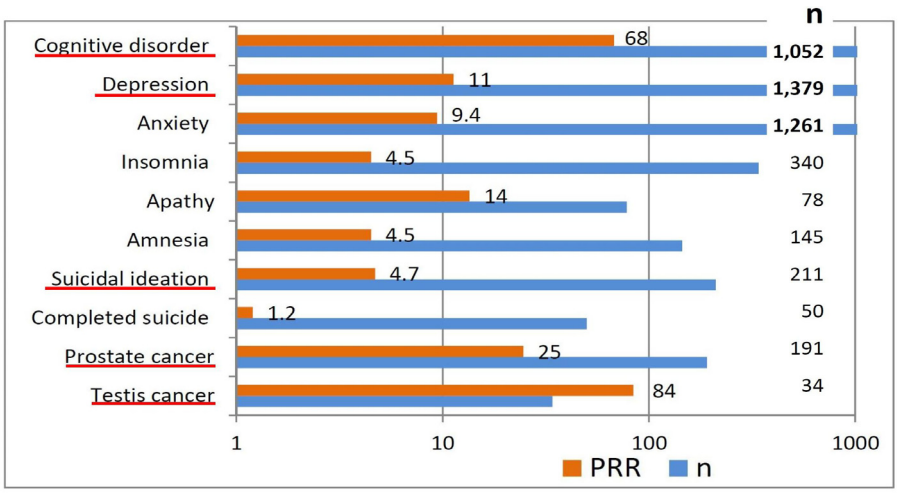
Table 5 : Prostatic cancer classified by modified Gleason score after 4-years treatment of prostatic hyperplasia with dutasteride

	year 2		year 4				
	Placebo	Duta-steride	Placebo	Duta-steride	OR OR	OR 95%CI	p value *b
Biopsy population (N)	3227	3225	2338	2442			
0(no abnormality)	2765	2069	2067	2224	1.34	1,11-1.61	0.002
Modified-GS 2-4	0	0	0	0	NA		
Modified-GS 5-6	390	286	214	148	0.64	0.52-0.80	<0.0001
Modified-GS 7	156	119	55	56	0.97	0.67-1.42	NS
Modified-GS 8-10*a	16	18	0	14	27.9	1,66-468	0.0001

*a : High grade prostatic cancer are not different by modified Gleason score (M-GS) at year 2 (18 and 17 in placebo and dutasteride group respectively).
However they were greatly different at year 4 (1 and 12 respectively: odds ratio was 11.5 (95%CI : 1.50-88.8, p=0.0035).
*b : p value is based of Fisher's exact test.

High grade prostatic cancers detected by the year 2 may be those that might have already existed but not detected by the baseline biopsy. On the other hand, high grade prostatic cancer detected at the year 4 may be de novo high grade cancers.

Figure 5: Common adverse reactions to finasteride and PRR Based on the FDA's ADR reports (data from http://rxisk.org/)



PRR: proportional reporting ratio (see Box 2)

● Common adverse reactions to finasteride and their proportional reporting ratios (PRR) based on the FDA's ADR reports (data from http://rxisk.org/) are shown in the Figure 5. Among them, cognitive disorders (n=1052, PRR=68), depression (n=1379, PRR=11), suicidal ideation (n=211, PRR=4.7), suicide completed (n=50, PRR=1.2) are noted. In addition, not only prostate cancers (n=191, PRR=25) but also testis cancer (n=34, PRR=84) should be noted.

● Mechanisms based on these psychiatric adverse reactions such as anxiety, depression and suicidal reactions may be related to the inhibition of synthesis of neurosteroids which is synthesized from testosterone [30]. Mukai (2008) reported that finasteride dose-dependently inhibits the stress-induced elevation of the brain allopregnanolone (AP) (a potent positive modulator of the $GABA_A$ receptors and one of the most important neurosteroids), and that a 10 mg/kg dose of finasteride can almost completely deplete AP in the rat brains [30].

● Although the treatment with Zagallo® is an intervention to a condition without threat to life, the harm induced by the treatment with Zagallo® may be life threatening with a possibility of high malignancy grade prostatic cancer and suicidal reactions, and may also cause non-life threatening serious adverse reactions such as sexual dysfunctions, cognitive disorders, psychiatric and neurological reactions.

Conclusion

Hence the harm clearly exceeds benefit. We do not recommend the use of this agent for androgenic alopecia.

Box 2: PRR (proportional reporting ratio) and ROR

- PRR: proportional reporting ratio. Ratio of proportions of adverse drug reaction (ADR) of concern (R) among all spontaneous reports for a medicinal product of concern (P) and all other medicinal products:
  PRR=(a/(a+b))／(c/(c+d))
- ROR: reporting odds ratio. Ratio of odds of ADR of concern (R)/all other reactions for a medicinal product of concern (P) and that of all other medicinal products:
  ROR(OR)=(a/b)／(c/d)
- P: a medicinal product of concern, R: An adverse reaction of concern

2 X 2 table for calculation of PRR and ROR

	Concerned ADR (R)	All other ADRs	Total ARDs
Concerned medicinal product (P)	a	b	a+b
All other medicinal products	c	d	c+d
All medicinal products	a+c	b+d	a+b+c+d

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Cochrane team comments on the ECDC draft advice on oseltamivir:

Criticising misinterpretation in the draft "Expert Opinion"

ECDC (European Centre for Disease Prevention and Control) announced on February 17 2016 that public consultation opened [1] on the draft "Expert Opinion on Neuraminidase inhibitors for the treatment and prophylaxis of influenza - Review of recent systematic reviews and meta-analyses" [2].

The recent systematic reviews and meta-analyses include the systematic review and meta-analysis by the Cochrane neuraminidase inhibitor team (Cochrane team) [3].

Hama et al [4], on behalf of the Cochrane team, submitted an expert opinion commenting that the draft advice and expert opinion by ECDC on neuraminidase inhibitors have many limitations including misunderstanding of the most important findings in the systematic review by the Cochrane team. The comments by Hama et al [4] covered comprehensive issues on the efficacy and safety of neuraminidase inhibitors, especially of oseltamivir as shown in the contents below.

The Cochrane team's comments [4] conclude as follows (See Supplementary material in detail):

Conclusion

As ECDC advice and expert opinion on neuraminidase inhibitor have many limitations including misunderstanding of the most important findings of our systematic review, meta-analysis and discussions.

We strongly recommend that our Cochrane review be re-read .

Findings from epidemiological studies should be taken into account.

Findings from basic sciences are also important to understand the mechanism of efficacy and harm from neuraminidase inhibitors:

Inhibition of host's neuraminidase followed by impaired functions of various cell such as immune, metabolic, renal, cardiac and neuronal cells by neuraminidase inhibitors is closely related not only to the symptom relief but also many adverse effects on various organs.

Central nervous system depressing and stimulating actions of oseltamivir but not zanamivir may be closely related to abnormal behaviours and sudden death from respiratory failure after oseltamivir use.

Finally, we find it strange that a public body would dismiss the findings of our Cochrane review and align its conclusions with a pharmaceutically-sponsored meta-analysis for which neither protocol nor assessment of risk of bias seems to exist.

Contents of comments by Cochrane team (Hama et al [4]: See supplementary material in detail):

1. On the analysis methods

1.1. On the principles of analysis methods in general
1.2. For the systematic review of treatment
1.2.1. The population: ITT population should be used for efficacy analysis.
1.2.2. Exclusion or inclusion of high dose groups
1.2.3. All hospitalizations
1.2.4. Pneumonia and bronchitis
1.2.5. Note that reduction of antibody production is related to the mechanism of action of symptom relief
1.2.6. Efficacy in non-influenza ILI
1.3. For the systematic review of prophylaxis: Discussions are needed by taking "false negative effect" into account both for ECDC advice and for our own.

2. On the data of individual results.

2.1. Treatment trials

2.1.1. Efficacy: complication especially on serious events leading to treatment withdrawal and hospitalization.

2.1.2. Harm: antibody production, QT interval, cardiovascular events.

2.1.2.1. Antibody production

2.1.2.2. QT interval and other cardiovascular events

2.1.2.3. Psychiatric events, injury and poisoning

2.2. Prophylaxis trials

2.2.1. Efficacy in prophylaxis trials:

2.2.2. Harm in prophylaxis trials:

2.2.2.1. Psychiatric reactions

2.2.2.2. Injury and poisoning

2.2.2.3. Other adverse reactions

2.2.2.3.1. Renal impairment

2.2.2.3.2. Hyperglycemic of diabetic events, and pain in limbs

2.2.2.3.3. Headaches

3. Evidence from non-randomized studies

3.1. Epidemiological studies suggesting neuropsychiatric adverse reactions to oseltamivir:

3.1.1. Prospective cohort studies and their systematic review and meta-analysis.

3.1.2. Proportional reporting ratio for abnormal behaviours especially of fatal outcome.

3.2. Adverse effects on mortality

3.2.1. Observational studies do not support protective effect on mortality

3.2.2. Epidemiological evidence suggesting sudden deterioration leading to death following oseltamivir use:

3.3. Adverse effect on pregnant women, fetus and newborns

4. No discussion on the mechanisms of action and reactions of oseltamivir

4.1. Oseltamivir act on the central nervous system (CNS) both as depressant and as stimulants.

4.1.1. Juvenile (7-day-old) rats and mature rats (intraduodenally and intravenously)

4.1.2. Oseltamivir has hypothermic effect on animals by inhibiting nicotinic acetylcholine receptor.

4.1.3. Oseltamivir induces abnormal behaviours by inhibiting MAO-A.

4.1.4. Oseltamivir has various other effects on CNS such as impairment of sensory system, impairment of cognition, impairment of alertness other than respiratory depression.

4.2. Oseltamivir has symptom relieving effects by inhibiting host' s endogenous neuraminidase, not by inhibiting viral load.

4.2.1 Label of oseltamivir does not state viral load reduction

4.2.2. Experiments indicate inhibition of host' s endogenous neuraminidase, but not viral load

4.3. Inhibiting host' s endogenous neuraminidase may be related with adverse effects of NIs

5. Efficacy and effectiveness in risk groups

6. Conflict of Interest

7. Conclusion

References

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