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Number comparison of medicines lists effective in the Republic of Tatarstan with the WHO model list of essential medicines: Do numbers matter?

Lilia E. Ziganshina*, Veronica N. Khaziakhmetova, Tatyana R. Abakumova and Elvira G. Alexandrova

Department of Clinical Pharmacology and Pharmacotherapy, Kazan State Medical Academy, Kazan, Russia

Abstract. A comparative analysis of positive medicines lists effective in the Republic of Tatarstan in 2009 was carried out to identify problems with development and functioning of 4 different lists. Comparison of listed medicine numbers revealed the extent of discrepancies requiring policy action. The discrepancies were uniform through the lists and reflected vulnerability to pharmaceutical promotion. It was concluded that development of national pharmaceutical policy was urgently needed to further implement the WHO Essential Medicines Concept.

Keywords: Essential Medicines, WHO Essential Medicines Concept, pharmaceutical policy

1. Introduction

The medicines situation in Russia changed dramatically since early 90th. The number of registered medicines kept increasing with every year. According to the Federal health-surveillance structure – Roszdravnadzor – 19 433 medicinal products were registered in Russia by March 2010 [18]. The attention of Government to pharmaceutical issues has dramatically increased: Governmental funds have been allocated and governmental projects of Supplementary medicines provision for selected patient categories and project "Health" have been initiated.

However, the question if these investments have contributed to health and longevity remains unanswered.

Paradoxically in the situation of the global financial crisis the medicine prices in Russia kept growing exceeding all highest world prices making out of pocket payments of Russian citizen and state medicines expenditures unprecedentally high. The latest update of the Russian Essential Medicines list aimed to tackle this medicine pricing disaster in the country and to regulate prices for essential medicines [14].

*Address for correspondence: Prof. Lilia E. Ziganshina, PhD, MD, Department of Clinical Pharmacology and Pharmacotherapy, Kazan State Medical Academy, 11 Mushtari Street, Kazan 420012, Russia. Tel.:/Fax: +7 843 273 0802; E-mail: lezign@mail.ru; lezign@gmail.com; Website: http://www.evidenceupdate-tatarstan.ru.

This is ironic in the view of the history of health care and Essential Medicines Concept development. After publication of the first WHO Model List of Essential medicines in 1977 [24], the World Health Assembly adopted its 31.32 resolution urging the member-states to develop national essential medicines lists in 1978. In the same year the International Conference on Primary care held in Alma-Ata (USSR) adopted the historical Alma-Ata Declaration on primary care [1], requiring immediate action from governments with focus on provision of essential medicines and vaccines as the most important component of required health system changes.

The WHO Model List of Essential medicines has been universally recognised as the basis for national lists regardless of countries' level of economical or social development [3]. The new time for the post-soviet countries with its changes required re-evaluation of strategic approaches to health and adoption of Essential medicines concept as the core component of the ongoing health reform.

With the aim to identify problems with development and functioning of medicines lists we sought to analyze positive medicines lists which have been officially in action in the health system of the Republic of Tatarstan in 2009 to contribute to the rational use of medicines and health system development.

2. Material and methods

We compared positive medicines lists effective on the territory of the Republic of Tatarstan (RT) in 2009 with the 16th WHO Model List of Essential Medicines (2009), WHO EML [22]. There are four positive medicines lists effective in RT:

A. The list of essential medicines approved by the Russian Federal Government (the order from 30 December, 2009) – Russian Essential Medicines List, REML [14].
B. The list of medicines served by prescriptions of a physician or physician's assistant for provision of supplementary free of charge medical care to designated categories of citizens, having rights to state social help (the order of the Ministry of health and social development of the Russian Federation dated 18 September, 2006 N 665 with later changes) – Russian Supplementary Medicines Lists, RSML [4].
C. The list of medicines, medicinal devices, specialized diet meals for the citizens entitled to provision of free of charge medicinal products, in accordance with the order of the government of Republic of Tatarstan N 315-p from 16 March, 2009 – Tatarstan Supplementary Medicines List, TSML [5].
D. The formulary list of medicines of the Republic of Tatarstan, 5th edition, 2009 – Tatarstan Formulary List, TFL [25].

In addition, we compared all the lists with each other by a methodology published elsewhere [26].

We used Microsoft Access for medicines lists comparisons and developed a database of medicines lists. To enable computer assisted comparisons we unified the names of medicines on the lists by manual editing of the lists in the Russian language. For example, we replaced the Russian name "nitroglycerine" with the international non-proprietary name (INN) "glyceryl trinitrate", we unified sequence of nouns and adjectives where appropriate. The editing process was carried out by two authors independently in a "blind" manner with subsequent manual matching of the edited lists. Altogether we formulated 25 queries to the database for coincidences on the lists and differences between the lists.

We analyzed the listing of medicines by medicine names (INNs, where available), dosage forms or formulations were not accounted for.

We calculated portions (percentages) of coincidences and differences. We performed quality analysis of differences according to the WHO Concept of Essential Medicines [3].

Table 1
Numbers of entries on positive medicines lists effective in the Republic of Tatarstan compared to the WHO Model List of Essential Medicines in the 21st century (by year)

WHO EML [22]		TFL		TSML		RSML		REML	
Year	Number	Year	Number	Year	Number	Year	Number	Year	Number
1999	308 [24]	2000 [25]	578					2000 [8]	421
2002	320 [24]	2002 [25]	665	2002 [19]	404			2002 [9]	505
2003	316							2003 [10]	531
		2004 [25]	669			2004 [13]	367	2004 [11]	427
2005	315					2005 [20]	525	2005 [12]	612
		2006 [25]	677			2006 [15]	445		
2007	320					2007 [21]	493	2007 [16]	658
		2008 [25]	695			2008 [4]	360		
2009	349			2009 [5]	278			2009 [14]	500

3. Results

3.1. General comparisons

The common feature was the increase in numbers of medicines on the analysed lists up to the year 2008 when the WHO EML was officially used as the Model for the Russian national Essential Medicine List (REML) development. The increase was nearly always continuous with exceptions of the year 2004 for the REML and the year 2006 for the Russian Supplementary Medicines List. The Tatarstan supplementary medicines list was updated only twice within the studied period of time (Table 1).

The average rates of lists expansion in terms of medicine numbers for the last decade were: 14.6 additional entries per year for the TFL; 33.9 – for the REML up to the 2009 update (2004 excluded); 42 – for the RSML up to the 2008 update (2006 excluded), as compared with 4.1 additional entries per year for the WHO EML. The expansion rates exceeded the WHO EML expansion rate by 3 times (TFL), by 8 times (REML), and by 10 times (RSML).

In the view of a well documented critical situation with research and development of principally new medicines of chemical synthetic or biotechnological origin in the 21 century [2, 23] despite huge financial investments, it seems possible that the major driving force of Russian list expansions has been the promotion of medicinal products by pharmaceutical companies, competing for quotas of state medicines budget to increase profits.

We identified 76 essential medicines (according to the WHO Model list) which were included on all 4 positive medicine lists effective in the Republic of Tatarstan (alphabet listing according to the Russian Cyrillic style):

1. azathioprine
2. azithromycin
3. allopurinol
4. amiodarone
5. amitriptyline
6. amoxicillin
20. hydrocortisone
21. hydroxycarbamide
22. hydrochlorothiazide
23. glibenclamide
24. glyceryl trinitrate
25. dacarbazine
39. mercaptopurine
40. metoclopramide
41. methotrexate
42. metronidazole
43. metformin
44. morphine
58. spironolactone
59. sulfasalazine
60. tamoxifen
61. timolol
62. phenobarbital
63. fludrocortisone

7. asparaginase
8. atenolol
9. acetazolamide
10. acetylsalicylic acid
11. acetylcysteine
12. aciclovir
13. beclometasone
14. betamethasone
15. budesonide
16. valproic acid
17. warfarin
18. verapamil
19. haloperidol
26. dexamethasone
27. diazepam
28. digoxin
29. doxycycline
30. ibuprofen
31. isosorbide dinitrate
32. ipratropium bromide
33. calcium folinate
34. carbamazepine
35. clotrimazole
36. levodopa + carbidopa
37. levothyroxine
38. mebendazole
45. nystatin
46. nifedipine
47. omeprazole
48. ondansetron
49. ofloxacin
50. pancreatic enzymes
51. paracetamol
52. penicillamine
53. pilocarpine
54. prednisolone
55. propranolol
56. ranitidine
57. salbutamol
64. fluconazole
65. fluphenazine
66. furosemide
67. chlorambucil
68. chlorpromazine
69. cefazolin
70. ciclosporin
71. cyclophosphamide
72. ciprofloxacin
73. enalapril
74. ethanol
75. etoposide
76. ethosuximide

Of particular interest were the WHO Essential medicines which were not listed on any of the analyzed acting positive lists. We identified 97 entries (see Appendix 1):
22 were vaccines and immunoglobulins, the nomenclature and use of which have been traditionally regulated in Russia by special alternative normative documents;
17 were intestinal anthelminthics, antifilarials, antigiardiasis, antischistosomals and antitrematode, antipneumocystosis and antitoxoplasmosis, antileishmaniasis and antileprosy medicines – medicines for diseases which do not present major public health problems in Russia;
12 were medicines for malaria, HIV-infection and tuberculosis (including fixed combinations); 10 were dermatological substances;
6 entries for contraceptive purposes; and
2 medicines for management of addictions – methadone and nicotine for replacement therapy.

The rest of not-listed medicines belonged to various therapeutic groups which have been represented in analysed documents by alternative analogous medicines.

It should be noted separately that the section "Medicines used in substance dependence programmes" has not been included on any of the analysed lists. Of particular notice is the methadone therapy, which should require special attention of regulatory authorities, and its potential inclusion would become possible only after updating the current or enacting new legislation.

4. Comparisons of individual lists

4.1. Tatarstan formulary list, TFL

The first Formulary list of the Republic of Tatarstan (Tatarstan Formulary List, TFL) was developed in 1999 (published in 2000) with expert, ideological, informational and methodological support from WHO-EURO. It included 578 medicines. The normative base for the lists development and the procedures for medicines selection were discussed, agreed and introduced in practice. On the turn of the Millennium the Republic of Tatarstan became the first region of the Russian Federation where the formulary system as a standardised process for medicine selection and use (monitoring medicine use and safety) was introduced in everyday health system functioning. However the second TFL (2002) included already 665 medicines,

the third (2004) – 669, the forth (2006) – 677, and the fifth (2008) – 695 names. The list expanded with its every update.

The TFL of the latest update (2008) included 695 medicines totally [25], following the WHO EML by 34% (234 of 695 entries), covering 67% of the Model list (234 of 349). Comparison with the REML revealed that the TFL followed the REML by 52% (359 of 695) covering 72% (359 of 500) of the REML.

The problems with the TFL:

The TFL included numerous examples of "me too" medicines – new medicinal products delivered to the market by pharmaceutical companies by a less costly route: by chemical rejiggering of well established molecules, crafting a new name, conducting a massive promotion campaign for the so called "newest innovative breakthrough" products [6]. We have identified 16 groups on the TFL which included the "me too" medicines with the numbers in brackets:

- $5HT_3$ receptors blockers (2);
- sulphonamides for diabetes mellitus: (5);
- low-molecular weight heparins: (3);
- calcium channel blockers (dihydropyridine derivatives): (3);
- ACE inhibitors: (6);
- angiotensin II receptors antagonists: (2);
- statins: (2);
- colony-stimulating factors: (3);
- NSAID, oxicams: (3);
- bisphosphonates: (4);
- general anaesthetics halogenised: (2);
- antidepressants, non-selective monoamine reuptake inhibitors: (3);
- antidepressants, SSRIs: (4);
- combination of long-acting beta 2 agonists with glucocorticoids: (2);
- anticholinergic broncholytics: (2);
- systemic antihistamines: (8).

The number of "me too" entries varied from 2 to 8 with the median of 3 [2, 4], and average of 3.38 ($\pm$1.71).

The TFL carried medicines inclusion of which had not been supported by scientific evidence of clinically meaningful outcomes as well as obsolete medicines; the examples include: cerebrolysin, cattle brain polypeptide extracts, actovegin, choline alfoscerate, hopatenic acid, glucosamine, chondroitine sulphate etc. The examples of medicines with unfavourable benefit/risk ratio include: nimesulide, hexoprenaline, vinpocetine etc. The TFL also included medicines developed and manufactured in Tatarstan: dimephosphone, vinibis, mebicar, xymedone.

4.2. Tatarstan Supplementary Medicines List, TSML

This list consisted of 278 medicines (test strips, bandages, etc. excluded from the analysis) from which 126 entries (45%) followed the WHO EML and 200 entries (72%) followed the REML. By these entries the TEML covered 36% of the WHO Essential medicines and 40% of the REML positions. The TSML included 152 medicines not meeting essentiality criteria of the WHO Model List. The pattern of these non-essential medicines reflected the same problems as in the TFL. The TSML included 78 medicines which were not on the REML.

4.3. Russian Essential Medicines List, REML

The latest update of the REML was historical by the fact of official recognition of the need to follow the WHO Model. For the first time in the new history the draft list was available publicly allowing potential consultation process prior to the final Governmental approval. Five hundred medicines by INN have been included on the REML of which 214 (43%) belong to the WHO Model list. These 214 entries cover 60% of the WHO Model List.

In the explanatory note to the draft REML, published prior to the REML's final approval by the Russian Government the following information was provided: amongst 500 entries on the REML 76 were medicines manufactured only in Russia, 261 – medicines produced both in Russia and abroad, and 163 medicines which were manufactured only by foreign pharmaceutical companies [17]. The listed medicines were represented by 2000 trade names and by more than 5500 dosage forms. The proportion of domestic products has increased up to 67% in comparison to the earlier version of the list published in 2007.

The 138 WHO Essential medicines which have not been included on the REML cover the 97 entries which we have described in general comparisons. Among 41 WHO essential entries that have been additionally omitted from the REML, but have been included on other positive lists noteworthy are the cheap mostly domestically produced essential medicines: Ferrous (II) salt, copper-containing intrauterine device, iodine, intermediate acting insulin, codeine, lithium carbonate, methionine, miconazole, sodium calcium edetate, neostigmine, nitrofutantoin, permethrin, promethazine, riboflavin, spectinomycin, streptokinase, sulfamethoxazole + trimethoprim, tetracaine, phytomenadione, folic acid, cefixime, and erythromycin. Obviously despite the fact that the latest version of REML has been developed for central price control mechanisms only, these medicines need to be considered for inclusion with the next update of the list. On the other hand we identified 285 medicines listed on the REML and not listed on the WHO EML. The inclusion of quite a few of these medicines has not been supported by existing evidence of effectiveness and safety, for example: ademethionine, alprostadil, betahistine, nandrolone, memanthine, zafirlukast, tioctic acid, etc. A number of medicines with unfavourable benefit/risk ratio were included on the REML, for example vinpocetine, hexoprenaline, rosiglitazone, sertindole, all of which have been heavily promoted in Russia.

4.4. Russian Supplementary Medicines List, RSML

Three hundred and sixty medicines by INN have been included on the latest update of the RSML. The analysis revealed that the RSML followed the WHO EML only in 26% of its entries (95 of 360) and it followed the REML in 59% of its entries (214 of 360). Thus the RSML covered 27% of WHO EML (95 of 349) and 43% of REML (214 of 500). We identified 265 medicines which were included on the RSML not listed on the WHO EML and 66 medicines which were not included on any of the analysed lists. The pattern of these non-essential medicines followed the pattern of the REML, but with much heavier presence of more expensive promoted medicines, such as rosuvastatin, salmeterole, fluvoxamine, rilmenidine, etc. Of particular notice should be the fact of inclusion of 4 additional to all the studied lists "me too" ACE inhibitors–quinapril, moexipril, spirapril, cilasapril, plus 3 ACE inhibitors/diuretic combinations, and of 4 additional to all the studied lists "me too" angiotensin II receptor antagonists–valsartan, irbesartan, eprosartan, candesartan, plus 2 combinations with diuretics.

Summing up, the analysis has shown that TSML had the highest percentage of WHO essential medicines on its listing and the TFL had the most broad WHO EML coverage.

The RSML had the lowest indices for both WHO essential medicines inclusion and the WHO EML coverage. The low WHO coverage by both studied lists for supplementary medicines provision may

Table 2
Percentages of inclusion of WHO essential medicines and WHO EML coverage by positive lists effective in the Republic of Tatarstan

TFL		TSML		RSML		REML	
% WHO essential medicines included	WHO EML coverage	% WHO essential medicines included	WHO EML coverage	% WHO essential medicines included	WHO EML coverage	% WHO essential medicines included	WHO EML coverage
34	67	45	36	26	27	42	60

reflect the practical purpose of the supplementary medicines supply – provision of medicines for out-patient services for designated categories of citizens. The REML by combination of these two indices had the most balanced position (see Table 2).

According to the estimates of the Commission on Macroeconomics and Health care (2001), it is possible to prevent more than 10 million of deaths a year by rational management of communicable and non-communicable diseases, pathological conditions in pregnancy, delivery and perinatal period. The majority of these measures are based on essential medicines [7].

For the Republic of Tatarstan, further procedural steps need to be introduced in practice in order to keep the lists and the development process to the WHO Model standard and fully implement the Essential Medicines concept. National pharmaceutical policy needs to be further developed.

5. Conclusions

- WHO Essential Medicines Lists have been successfully used in the health system of the Republic of Tatarstan as a model instrument since 1999.
- The number comparison revealed discrepancies between the lists which require urgent development of national pharmaceutical policy based on the WHO Essential medicines Concept.
- The content discrepancies are uniform through the positive lists effective in the Republic of Tatarstan with the Russian supplementary medicines list (RSML) being the most problematic and reflect the vulnerability to pharmaceutical promotion.
- Policy recommendations for the health system of the Republic of Tatarstan include revision of the Tatarstan supplementary medicines list (TSML) and the formulary list (TFL) on the basis of the WHO EML with fast-track deletion of medicines not meeting the WHO essentiality criteria, further development of selection process according to the WHO model, and introduction of state pharmaceutical policy.

Conflict of interest statement

Authors declare that there is no conflict of interest.

Acknowledgement

We would like to thank Natalia M. Ofitserova for expert assistance with development of computer-based model for medicines lists comparisons.

Appendix 1

Vaccines and immunoglobulins

1. BCG vaccine
2. cholera vaccine
3. diphtheria vaccine
4. hepatitis A vaccine
5. hepatitis B vaccine
6. haemophilus influenzae type b vaccine
7. influenza vaccine
8. Japanese encephalitis vaccine
9. measles vaccine
10. meningococcal meningitis vaccine
11. mumps vaccine
12. pertussis vaccine
13. pneumococcal vaccine
14. poliomyelitis vaccine
15. rabies vaccine
16. rotavirus vaccine
17. rubella vaccine
18. tetanus vaccine
19. typhoid vaccine
20. varicella vaccine
21. yellow fever vaccine
22. antivenom immunoglobulin*

Intestinal anthelminthics, antifilarials, antileishmaniasis, antigiardiasis, antischistosomals and antitrematode, antipneumocystosis and antitoxoplasmosis, antileishmaniasis, and antileprosy medicines

23. albendazole
24. benznidazole
25. nifurtimox
26. eflornithine
27. melarsoprol
28. oxamniquine
29. suramin sodium
30. triclabendazole
31. sodium stibogluconate or meglumine antimoniate
32. paromomycin
33. pentamidine
34. niclosamide
35. diloxanide
36. diethylcarbamazine
37. ivermectin
38. clofazimine
39. sulfadiazine

Malaria, tuberculosis and HIV medicines, including the fixed dose combination

40. isoniazid + rifampicin + ethambutol
41. emtricitabine + tenofovir
42. efavirenz + emtricitabine + tenofovir
43. emtricitabine
44. lamivudine + nevirapine + stavudine
45. tenofovir disoproxil fumarate
46. lamivudine + nevirapine + zidovudine
47. amodiquine
48. artemether
49. artemether + lumefantrine
50. artesunate
51. proguanil

Dermatologic agents

52. aluminium diacetate
53. benzoic acid + salicylic acid
54. coal tar
55. dithranol
56. podophyllum resin
57. calamine lotion
58. selenium sulfide
59. silver sulfadiazine
60. methylrosanilinium chloride (gentian violet)
61. neomycin sulfate + bacitracin

Contraception means

62. condoms
63. diaphagms
64. estradiol cypionate+medroxyprogesterone acetate
65. medroxyprogesterone acetate
66. norethisterone enantate
67. levonorgestrel-releasing implant

Medicines used in substance dependence programmes

68. methadone
69. nicotine replacement therapy (NRT)

Vitamins and minerals

70. sodium fluoride
71. nicotinamide

Antidotes

72. potassium ferric hexacyano-ferrate(II)–2H20 (prussian blue)
73. methylthioninium chloride (methylene blue)
74. sodium nitrite

Antibacterials

75. cloxacillin
76. procaine benzylpenicillin
77. trimethoprim

Disinfectants and antiseptics

78. glutaral
79. chloroxylenol
80. chlorine base compound

Muscle relaxants

81. alcuronium
82. vecuronium

Antacids

83. aluminium hydroxide
84. magnesium hydroxide

Cardiovascular medicines

85. amiloride
86. hydralazine

Medicines for children

87. acetic acid (ENT)
88. prostaglandin E (neonatal care)

Antianaemia medicines

89. hydroxocobalamin
90. iron [II] salt + folic acid

Local anaesthetics

91. lidocaine + epinephrine

Diagnostic agents

92. meglumine iotroxate

Antifungal agents

93. flucytosine

Antithyroid medicines

94. propylthiouracil

Parenteral medicines

95. glucose with sodium chloride

Antiallergics medicines

96. chlorphenamine

Medicines used in diarrhoea

97. zinc sulfate

References

[1] Declaration of Alma-Ata. International Conference on Primary Health Care, Alma-Ata, USSR, 6–12 September 1978, 3 p. http://www.who.int/hpr/NPH/docs/declaration_almaata.pdf (accessed August 2010).

[2] E. Fleming, Ph. Ma, From the analyst's couch: Drug life-cycle technologies, *Nature Reviews Drug Discovery* **1**, 751–752 (October 2002). doi:10.1038/nrd926

[3] H.V. Hogerzeil, The concept of essential medicines: Lessons for rich countries, *BMJ* **329** (2004), 1169–1172.

[4] http://base.garant.ru/12149709/#1000; http://www.consultant.ru/online/base/?req=doc;base=LAW;n=84391 (accessed August 2010).

[5] http://prav.tatar.ru/rus/docs/post/rasp1.htm?page=7&pub_id=28083 (accessed August 2010).

[6] http://stanmed.stanford.edu/2005summer/drugs-metoo.html (accessed August 2010).

[7] http://whqlibdoc.who.int/publications/2001/924154550x.pdf (accessed August 2010).

[8] http://www.consultant.ru/online/base/?req=doc;base=LAW;n=26246 (accessed in August 2010).
[9] http://www.consultant.ru/online/base/?req=doc;base=LAW;n=36167 (accessed in August 2010).
[10] http://www.consultant.ru/online/base/?req=doc;base=LAW;n=41426 (accessed in August 2010).
[11] http://www.consultant.ru/online/base/?req=doc;base=LAW;n=49980 (accessed in August 2010).
[12] http://www.consultant.ru/online/base/?req=doc;base=LAW;n=57669 (accessed in August 2010).
[13] http://www.hemophilia.ru/.../medzakon.html (accessed in August 2010).
[14] http://www.minzdravsoc.ru/docs/government/26 (accessed August 2010).
[15] http://www.rg.ru/2006/.../lekarstva-perechenj-dok.html (accessed in August 2010).
[16] http://www.rg.ru/2007/04/06/lekarstva.html (accessed in August 2010).
[17] http://www.rosapteki.ru/order/arhiv/detail.php?ID=31321 (accessed August 2010).
[18] http://www.roszdravnadzor.ru/registration/ls/spis (accessed 5 March 2010).
[19] http://www.rt-online.ru/ (accessed in August 2010).
[20] http://www.rusmg.ru/php/content.php?id=5765 (accessed in August 2010).
[21] http://www.tatar.ru/rus/zdrav/spisok.htm, Copyright 2006–2010 Кабинет министров Республики Татарстан (accessed in August 2010).
[22] http://www.who.int/medicines/publications/essentialmedicines/en/index.html, http://www.who.int/topics/essential_medicines/ru/, http://www.who.int/selection_medicines/committees/expert/17/sixteenth_adult_list_en.pdf (accessed August 2010).
[23] B. Hughes, FDA drug approvals, *Nature Reviews Drug Discovery* **9** (February 2010), 89–92, doi:10.1038/nrd3101, http://www.nature.com/nrd/journal/v9/n2/full/nrd3101.html
[24] R. Laing, B. Waning, A. Gray, N. Ford and E. 't Hoen, 25 years of the WHO essential medicines lists: Progress and challenges, *Lancet* **361** (2003), 1723–1729.
[25] *Republican Drug Formulary: Hand-Book of Trade Names, Dosage Forms and Classification*, 5th edition, updated, Approved by the Ministry of Health, F.F. Yarkaeva, ed, Kazan, Medicina, 2009, 180 pp.
[26] L.E. Ziganshina, R.R. Niyazov and A.F. Titarenko, Methodology guidelines on clinical pharmacology analysis (ATC/DDD, indicator analysis, pharmacoepidemiology methods, consumption of domestic versus imported medicines, WHO Model EML comparison, supplementary drug supply), Kazan, 2008, 55 pp.

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Erratum

Making medical practice safer: The role of public policy

S.E.D. Shortt, Michael F. Green, Stan Corbett, Laure Paquette, Nadia Zurba and Margaret Darling

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The second author of this article is Michael E. Green, not Michael F. Green as originally mentioned.

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Cerebrolysin for acute ischaemic stroke[1,2,3]

Lilia E. Ziganshina*, Tatyana Abakumova and Alexandra Kuchaeva
Department of Clinical Pharmacology and Pharmacotherapy, Kazan State Medical Academy, Kazan, Russian Federation

Abstract. *Background*: Cerebrolysin is a mixture of low-molecular-weight peptides and amino acids derived from pigs' brain tissue which has proposed neuroprotective and neurotrophic properties. It is widely used in the treatment of acute ischaemic stroke in Russia and China.

Objectives: To assess the benefits and risks of cerebrolysin for treating acute ischaemic stroke.

Search strategy: We searched the Cochrane Stroke Group Trials Register (February 2009), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2009), MEDLINE (1966 to February 2009), EMBASE (1974 to February 2009), LILACS (1982 to February 2009), Science Citation Index (1940 to February 2009), SIGLE Archive (1980 to March 2005), and a number of relevant Russian Databases (1988 to February 2009). We also searched reference lists, ongoing trials registers and conference proceedings.

Selection criteria: Randomised controlled trials comparing cerebrolysin with placebo or no treatment in patients with acute ischaemic stroke.

Data collection and analysis: Three review authors independently applied the inclusion criteria, assessed trial quality and extracted the data.

Main results: We included one trial involving 146 participants. There was no difference in death (6/78 in the cerebrolysin group versus 6/68 in the placebo group; risk ratio (RR) 0.87, 95% confidence interval (CI) 0.29 to 2.58) or in the total number of adverse events (16.4% versus 10.3%; RR 1.62, 95% CI 0.69 to 3.82) between the treatment and control groups.

Conclusions: There is not enough evidence to evaluate the effect of cerebrolysin on survival and dependency in people with acute ischaemic stroke. High-quality and large-scale randomised controlled trials may help to gain a better understanding of the potential value of cerebrolysin in acute ischaemic stroke.

Keywords: Amino acids, neuroprotective agents, stroke

1. Background

Stroke is the brain equivalent of a heart attack, which occurs when the brain loses its blood and energy supply resulting in damage to brain tissue. Stroke is one of the major causes of disability and mortality all over the world [1, 13, 14]. More than 50% of survivors of acute stroke experience severe neurological

*Address for correspondence: Lilia E. Ziganshina, Department of Clinical Pharmacology and Pharmacotherapy, Kazan State Medical Academy, 11 Mushtari Street, 420012, 14-15 Malaya Krasnaya Street, 420015 Kazan, Tatarstan, Russian Federation. E-mail: lezign@mail.ru; lezign@gmail.com.

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disorders (loss of vision or speech or both, paralysis and confusion) and these are not restored in 30% to 66% of cases six months after a stroke [21]. Annually, 15 million people worldwide suffer a stroke. Of these, five million die and another five million are left permanently disabled, placing a burden on family and community [71]. There are 10,000 cases of acute stroke registered in the Russian Federation annually. In 2001, stroke morbidity reached 3.36 per 1000 population with a mortality rate of 40.37% (61.4% for haemorrhagic stroke and 21.8% for ischaemic stroke). The north-west regions had the highest morbidity of 7.43 per 1000, followed by some cities in middle areas (5.37 per 1000) and the far east (4.41 per 1000) [26, 65].

1.1. Pharmacological treatment options

Effective, simple and reliable treatment methods are urgently needed to decrease stroke mortality and disability. Many clinical trials and Cochrane reviews have addressed the question of benefits and risks of potential pharmacological treatment options for acute ischaemic stroke. However, such strategies with proven therapeutic effects and an acceptable benefit-to-risk ratio are still lacking. Potential strategies could be grouped according to the existing evidence of their benefits and harms.

1.2. Potential benefits

Aspirin appears to be the only treatment that has been shown to be effective when started within 48 hours of onset of ischaemic stroke for early secondary prevention [53]. Thrombolysis with intravenous recombinant tissue plasminogen activator presents a promising strategy, but only in experienced centres and in highly selected patients [70]. The evidence has been insufficient so far to identify a preferred thrombolytic agent, the dose, route of administration and the latest time window [42, 70]. Another Cochrane review of trials performed in the pre-controlled trial era suggested a favourable effect of glycerol treatment on short-term survival in ischaemic stroke patients [50]. Fibrinogen-depleting agents seem to be promising although more data are needed [39].

1.3. Potential harms

Tirilazad, an amino steroid inhibitor of lipid peroxidation, increased the combined end-point of 'death or disability' in patients with acute ischaemic stroke [64]. Lubeluzole, an ion channel modulator of glutamate release that has a benzothiazole structure with proposed neuroprotective properties, did not reduce death or dependency in acute ischaemic stroke patients. In contrast, it increased heart-conduction disorders (Q-T prolongation) [23].

1.4. Evidence of lack of benefit has accumulated for the following potential pharmacotherapeutic strategies

Calcium antagonists [31]; haemodilution [3]; excitatory amino acid antagonists, including ion channel modulators and N-methyl-D-aspartic acid (NMDA) antagonists [44]; anticoagulant therapy, which was not associated with net short or long-term benefits [25] and did not offer net advantages over antiplatelet agents [10]; piracetam [49]; and a free radical trapping agent NXY-059 [59].

1.5. Evidence from randomised controlled trials is insufficient for conclusions of benefit or harm in the following interventions

Glycoprotein IIb-IIIa inhibitors [17]; ginkgo biloba [77]; naftidrofuryl, a 5-HT2 serotonergic antagonist [38]; low-molecular-weight heparins or heparinoids [54]; theophylline or methylxanthine derivatives [6, 5]; mannitol [9]; nitric oxide donors [7]; blood pressure altering [11, 12]; prostacyclin and its analogues [4]; vinpocetine [8]; corticosteroids [47] and gangliosides [15].

1.6. Neuroprotection as a potential strategy

The term 'neuroprotection' is used to describe the putative effect of interventions protecting the brain from pathological damage. In ischaemic stroke the concept of neuroprotection includes inhibition of pathological molecular events leading to calcium influx, activation of free radical reactions and cell death. Knowledge of pathophysiology in acute ischaemic stroke stimulated development of a number of potential neuroprotective agents. Many neuroprotective agents have proven to be efficacious in animal studies. Demonstration of benefit in patients with acute ischaemic stroke on clinically relevant outcomes continues to be a challenge. Cerebrolysin is a mixture of low-molecular-weight peptides (80%) and free amino acids (20%) derived from pigs' brain tissue, with proposed neuroprotective and neurotrophic properties similar to naturally occurring growth factors (nerve growth factor, brain-derived neurotrophic factor) [2, 20].

Results of in vitro and animal studies of cerebrolysin suggest its potential for treating acute ischaemic neuronal damage. For example, cerebrolysin was shown to be effective in tissue culture models of neuronal ischaemia dose-dependently increasing neuronal survival [56]. In brain slices it counteracted necrotic and apoptotic cell death induced by glutamate [51]. Cerebrolysin also demonstrated neuroprotective activity in a rat model of haemorrhagic stroke [40] and spinal cord trauma [55].

Yet, despite the effectiveness of neuroprotective agents in animal models of stroke, clinical trials of neuroprotective agents in humans have provided disappointing results [19]. More recent Cochrane reviews of effects of individual neuroprotective agents and pharmacological groups confirmed this [23, 44, 49, 64]. Other means of neuroprotection are being sought. Some neuroprotective agents show beneficial effects on post-hoc analyses, and some studies are still ongoing [68]. The potential of cerebrolysin for Alzheimer's disease has been systematically reviewed [20]. Cerebrolysin is well accepted by Russian physicians. It is widely used in the treatment of acute ischaemic stroke and other neurological disorders [16, 24, 46]. Research data from observational studies and clinical trials of cerebrolysin in acute stroke or head injury, with the majority of them carried out in Russia, have accumulated [16, 22, 24, 36, 63, 72]. There is a need for a systematic evaluation of these results.

The aim of this review is to verify whether the available evidence from controlled trials is in favour of a beneficial effect of cerebrolysin for acute ischaemic stroke.

2. Objectives

1. To assess the benefits and risks of cerebrolysin for treating acute ischaemic stroke.
2. To estimate the effect of cerebrolysin on survival and disability.
3. To assess serious adverse events and adverse effects.

3. Methods

3.1. Criteria for considering studies for this review

3.1.1. Types of studies

We included all randomised controlled trials (RCTs), published or unpublished, comparing cerebrolysin with placebo or no treatment in patients with acute ischaemic stroke. We excluded uncontrolled studies, as well as quasi-randomised controlled trials where allocation to treatment or control was not concealed (e.g. allocation by alteration, open random number list, date of birth, day of the week or hospital number).

3.1.2. Types of participants

People with acute ischaemic stroke, irrespective of age, gender, or social status, whose symptom onset was less than 48 hours previously.

3.1.3. Types of interventions

We planned to compare cerebrolysin or newer peptide-mixtures, which we have named 'cerebrolysin-like agents', with placebo or no treatment. We also planned to compare cerebrolysin or cerebrolysin-like agents added to standard treatment versus standard treatment alone. Standard treatment is not defined precisely and may differ between studies. Study medication must have been started within 48 hours of stroke onset and must have continued for at least two weeks. If trials of cerebrolysin versus other neuroprotective agents are identified in future we will add a separate analysis for this comparison.

3.1.4. Types of outcome measures

3.1.4.1. Primary

1. Poor functional outcome defined as death or dependence at the end of the follow-up period.
2. Early death (within two weeks of stroke onset).

3.1.4.2. Secondary

1. Quality of life, if assessed in the included studies.
2. All-cause death.
3. Time to restoration of capacity for work.

3.1.4.3. Adverse events and effects

1. Serious adverse events: fatal, life threatening, requiring hospitalisation or change of treatment regimen.
2. Adverse effects specifically associated with cerebrolysin, such as hypersensitivity reactions.
3. Total number of adverse events.

3.2. Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module.

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor in February 2009, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane*

Library, Issue 1, 2009), MEDLINE (1966 to February 2009) (see Appendix 1), EMBASE (1974 to February 2009), LILACS Database (Latin American and Caribbean Health Sciences Literature) (1982 to February 2009), Science Citation Index (1940 to February 2009), SIGLE (System for Information on Grey Literature in Europe) (http://opensigle.inist.fr/) (1980 to March 2005), and the following Russian Databases (1988 to February 2009): Rossiyskaya medicina (http://www.scsml.rssi.ru) and Otkritiy medicinskiy club (http://www.medart.tomsk.ru).

In an effort to identify further published, unpublished and ongoing trials and obtain additional trial information we:

1. checked the reference lists of all trials identified by the above methods;
2. searched the following neurology conference proceedings held in Russia: Chelovek i Lekarstvo (2006 to 2009), National'niy congress cardiologov (2006 to 2009), Rissiyskiy Megdunarodniy Congress Cerebrovascularnaya patologiya i insult (2008 to 2009);
3. searched the following ongoing trials and research registers: The Stroke Trials Registry (http://www.strokecenter.org/trials/), ClinicalTrials.gov (http://clinicaltrials.gov/) and Current Controlled Trials (http://www.controlled-trials.com/).

We attempted to identify all relevant studies regardless of language. We had planned to contact two pharmaceutical companies but this was not done.

3.3. Data collection and analysis

3.3.1. Study selection

At least two review authors independently examined all citations and their abstracts and established their relevance and the need to acquire the full article. In cases of uncertainty we obtained the full article. We independently applied the inclusion criteria and resolved disagreements through discussion with all three review authors. All three authors examined the full text of study reports. We only included those studies that met the pre-determined inclusion criteria. We excluded studies that did not meet the inclusion criteria and explained the reason for exclusion in the Characteristics of excluded studies table (Table 1).

3.3.2. Assessment of methodological quality

All three review authors independently evaluated methodological quality in terms of generation of allocation sequence, allocation concealment, blinding, loss to follow-up of participants and other risks of bias. We made judgments on generation of allocation sequence, allocation concealment, blinding and other risks of bias as adequate (yes), inadequate (no), or unclear, and presented quotes to support our judgments in the Risk of bias table partition in the Characteristics of the included study table (Table 2). We considered loss to follow-up to be acceptable if it was less than 10%. We resolved any disagreements arising at any stage by discussion or with a third party when necessary.

3.3.3. Data extraction

All three review authors independently extracted data using a standardised data extraction form. We extracted data on the methods of studies, participants, interventions, and outcomes. We resolved any differences in the extracted data by referring to the original articles and through discussion or by consulting the third party. We extracted data to allow an intention-to-treat analysis (including all the participants

Table 1
Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Cuparnecu 2001 [18]	Reported as an abstract only; no information on follow-up
Haffner 2001 [27, 28]	Reported as an abstract only; efficacy assessment with stroke scales; no information on death
Hong 2002 [29]	Cerebrolysin used in rehabilitation after ischaemic stroke
Hong 2005 [30]	Cerebrolysin used for 10 days (protocol specifies 14 days); efficacy assessment with stroke scales
Jin 1999 [32]	Cerebrolysin compared with xingnaojing
Kulchikov 2008 [33]	Reported as an abstract only Not a relevant research question: Viral complications of stroke
Kulchikov 2008a [34]	Reported as an abstract only Not a relevant research question: Infection complications of stroke (pneumonia)
Makarenko 2006 [41]	Reported as an abstract only Not a relevant research question: Cerebrolysin used to treat infection complications (pneumonia) in patients with stroke
Ren 2002 [48]	Confounded study: Disodium cytidine triphosphate or cerebrolysin used for 10 days
Sagatov 2008 [52]	Reported as an abstract only Not a relevant research question or comparison: Cerebrolysin plus emoxepine versus cerebrolysin
Shamalov 2006 [57]	Reported as abstract only; cerebrolysin used for 10 days
Shi 1990 [58]	Cerebrolysin used in patients with cerebral haemorrhage
Skvortsova 2004, 2005 [62, 63]	Cerebrolysin used for 10 days
Skvortsova 2008 [60, 61]	Reported as an abstract only MRI infarct volume as efficacy measure
Vilensky 2000 [66]	Cerebrolysin used for 5 days
Vilensky 2006 [67]	Reported as an abstract only Cerebrolysin compared with cerebrolysin administered via different routes
Wang 1997 [69]	Cerebrolysin in combination with nitrendipine, glucose and insulin compared with salvia miltiorrihiza in combination with low-molecular-weight dextran
Wu 1995 [73]	Reported as an abstract only Cerebrolysin used in combination with urokinase
Yavorskaya 2008 [74]	Reported as an abstract only Not a relevant research question: Participants with cognitive disorders
Zhang 1994 [76]	Too small (27 patients), probably a non-randomised trial
Zhang 1997 [75]	Not a relevant research question or comparison: Cerebrolysin used in combination with speaking training, mannitol and conventional therapy versus conventional therapy and mannitol
Zhu 2003 [78]	Cerebrolysin used in patients with stroke episode duration of 28 ± 7 days; efficacy assessment with stroke scales

MRI: Magnetic resonance imaging.

in the groups to which they were originally randomly allocated). We calculated the percentage loss to follow-up and presented it in the Risk of bias table partition in the Characteristics of the included study table (Table 2).

For binary outcomes, we extracted the number of participants with the event in each group. For continuous outcomes, we planned to use arithmetic means and standard deviations for each group.

Table 2
Characteristics of included studies Ladurner 2005 [36]

Methods	Multicentre, randomised, double-blind controlled trial 25 participants (17%) were lost to follow up Mean duration of follow-up: 90 days
Participants	146 participants randomised, 121 evaluated Inclusion criteria: Men and women with their first acute ischaemic stroke with clinical symptoms of middle cerebral artery area, aged 45 to 85 years, admitted to hospital and started on medication within 24 hours after stroke onset, with a Glasgow Coma Score >10 and a Canadian Neurological Scale score between 4.5 and 8.0 at baseline Exclusion criteria: Haemorrhagic stroke, transient ischaemic attacks, uncontrollable hypertension, acute myocardial infarction, congestive heart failure, moderate to severe dementia prior to stroke, stupor or coma, severe concomitant diseases, impaired renal function, history of prior stroke
Interventions	Intervention: Cerebrolysin 50 ml (mixed with 50 ml normal saline) by intravenous infusion over 20 minutes for 21 days after admission to the hospital in addition to basic therapy (78 participants) Control: Placebo (100 ml normal saline) by intravenous infusion over 20 minutes for 21 days after admission to hospital in addition to basic therapy (68 participants) Basic therapy: Pentoxifylline (300 mg/day intravenously) and acetylsalicylic acid (250 mg/day orally) for the first 21 days; pentoxifylline (2 × 400 mg/day orally) and acetylsalicylic acid (250 mg/day orally) from days 22 to 90
Outcomes	1. Efficacy measures: Canadian Neurological Scale (CNS), Barthel Index (BI), Glasgow Coma Scale (GCS), Clinical Global Impression (CGI), Mini-Mental State Examination (MMSE), Syndrome Short Test (SST), Self Assessment Scale, and the Hamilton Rating Scale for Depression (HAMD) performed at baseline and at all subsequent study visits on days 1, 3, 7, 14, 21, and 90 2. Adverse events, including abnormal laboratory findings and changes in clinical laboratory tests, changes in vital signs and general physical and neurological examinations rated as mild, moderate and severe 3. All-cause mortality reported as serious adverse events
Notes	Location: 8 sites in Austria, the Czech Republic and Hungary Cerebrolysin and the randomisation procedure was provided by the manufacturer of cerebrolysin, EBEWE Pharma
Risk of bias	

Item	Authors' judgement	Description
Allocation concealment?	Yes	Quote: 'For each patient a sealed envelope with information on the actual treatment dispensed was provided to the investigator for emergency cases. All envelopes remained sealed throughout the study'
Blinding?	Yes	Quote: 'The investigators and all other study personnel were blind as to the random code assignment until the completion of the statistical analysis' Comment: Impossible to assess blinding by outcomes
Adequate sequence generation?	Yes	Quote: 'Patients who met all entry criteria were assigned to the treatment groups in a 1 : 1 ratio, according to a randomisation code generated by computer software (EBEWE Pharma, Unterach, Austria). The randomisation was carried out in blocks of 12 patients stratified by study centre'
Incomplete outcome data addressed?	Unclear	Comment: Not applicable because the information on the outcomes that are of interest in the review was available only for serious adverse events including death 25 participants out of 146 randomised were lost to follow up (17%)
Free of selective reporting?	Unclear	Comment: Not applicable because the information on the outcomes that are of interest in the review was available only for serious adverse events including death
Free of other bias?	No	17% lost to follow up Manufacturer of cerebrolysin provided the medication and randomisation codes (procedure)

3.3.4. Data analysis

We undertook analysis according to the intention-to-treat principle. We planned to use the Review Manager software to analyse the data (RevMan 2008) [45]. We planned to use relative risk as a measure of effect for binary outcomes. For continuous data, we planned to use the mean difference (MD). If appropriate, we planned to calculate a summary statistic for each outcome. We planned to test for homogeneity of effect sizes between studies using the I^2 test for heterogeneity. If heterogeneity was present ($P < 0.1$), and the number of studies permitted, we planned to investigate it using the following subgroups:

1. dose of cerebrolysin;
2. length of treatment.

In cases where it was appropriate to pool data and heterogeneity was detected, we planned to use the random-effects model.

We planned to perform a sensitivity analysis to test the robustness of the results. We planned to investigate the effect of methodological study quality (low, moderate, or high risk of bias) using a sensitivity analysis. We planned to use funnel plots to examine asymmetry, which may have been caused by publication bias or heterogeneity.

4. Results

4.1. Description of studies

The searches identified 23 RCTs for possible inclusion. We excluded 22 of these studies because: (1) the outcomes reported were only either impairment scales or the number of participants with neurological improvement without any of the predefined outcome measures, (2) the study medication was not started within 48 hours of stroke onset and had not been continued for at least 14 days, (3) the research questions were not relevant, (4) the studies used different comparisons, or (5) the studies were reported as abstracts only [18, 27–30, 32–34, 41, 48, 52, 57, 58, 60–63, 66, 67, 69, 73–76, 78]. We have presented the reasons for exclusion in the Characteristics of excluded studies table (Table 1).

Only one trial met the inclusion criteria [36]. This was a multicentre placebo-controlled study conducted in Austria, the Czech Republic and Hungary supported by the manufacturer of cerebrolysin, EBEWE Pharma. The trial described the distinct inclusion and exclusion criteria. The average age of participants in the two comparison groups was 65 years. The trial randomised 146 participants within 24 hours of stroke onset to either the treatment group (cerebrolysin plus basic therapy; 78 participants) or to the control group (placebo plus basic therapy; 68 participants). There were no significant differences between the two groups in terms of baseline characteristics. In the treatment group, cerebrolysin was administered intravenously once a day in a dose of 50 ml over a period of 20 minutes for 21 days. Cerebrolysin was provided to the study centres by EBEWE Pharma. Placebo consisted of 100 ml normal saline. The same basic therapy was used in the treatment group and the control group (pentoxifylline and acetylsalicylic acid).

The outcome measures used were the Canadian Neurological Scale (CNS), the Barthel Index (BI), the Glasgow Coma Scale (GCS), the Clinical Global Impression (CGI), the Mini-Mental State Examination (MMSE), the Syndrome Short Test (SST), the Self Assessment Scale, and the Hamilton Rating Scale for Depression (HAMD) – performed at baseline and at subsequent visits on days one, three, seven, 14, 21, and 90. Adverse effects included abnormal laboratory findings and changes in clinical laboratory tests,

changes in vital signs, and general physical and neurological examinations rated as mild, moderate and severe. The numbers of participants who died during the study period in both the cerebrolysin group and the placebo group were reported in the safety section of the paper. We used these numbers to assess all-cause death. The duration of follow-up was 90 days; 25 participants (17%) were lost to follow up, nine of which were in the treatment group and the remaining sixteen were in the control group. We present details of the included trial in the Characteristics of included study table (Table 2).

There are no trials awaiting assessment and we are not aware of any ongoing trials.

4.2. Risk of bias in included studies

Only one RCT met the inclusion criteria. The manufacturer of cerebrolysin, EBEWE Pharma, provided the randomisation method: Computer-generated randomisation code. Sealed envelopes allowed for allocation concealment and remained sealed throughout the study. Investigators and all study personnel were blinded. However, it was impossible to assess blinding by outcome. Twenty-five participants out of 146 randomised were lost to follow up (17%). We compared by intention-to-treat principle the number of deaths extracted from the safety section of the trial report and presented data as all-cause death without performing any analysis [36].

4.3. Effects of interventions

The study did not report on the primary outcome measures, such as poor functional outcome (defined as death or dependence at the end of the follow-up period) and early death (within two weeks of stroke onset). It did not report on any of the secondary outcomes measures: Quality of life, all-cause death and time to restoration of capacity for work. We used the data on the number of deaths in both groups to generate the secondary outcome of all-cause death. Six participants (six of 78 randomised) died in the cerebrolysin group and six participants died in the placebo group (six of 68 randomised). We calculated the risk ratio for the extracted outcome all-cause death: RR 0.87, 95% CI 0.29 to 2.58 (Fig. 1, Table 3). The trialists reported on the following causes of death: Cerebral infarct (four in the cerebrolysin group and two in the placebo group), heart failure (two in the cerebrolysin group and one in the placebo group), pulmonary embolism (two in the placebo group), pneumonia (one in the placebo group). The trialists did not report on the time when those deaths occurred.

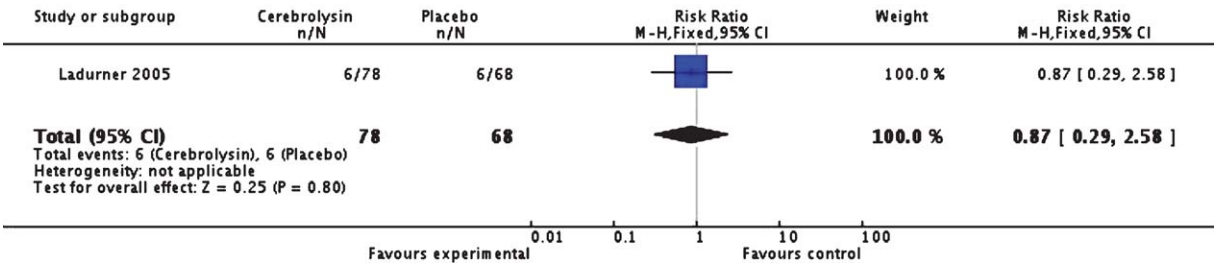

Fig. 1. Cerebrolysin versus placebo, Outcome 1 All-cause death.

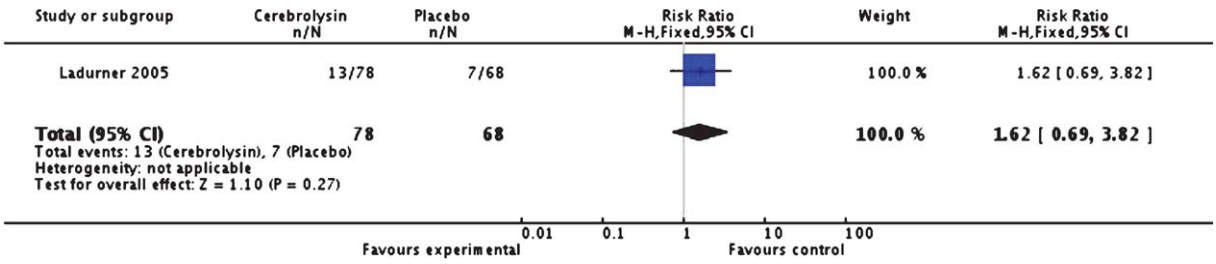

Fig. 2. Cerebrolysin versus placebo, Outcome 2 Total number of adverse events.

4.3.1. Adverse events and effects

The trialists reported the overall incidence of adverse events: 16.4% in the cerebrolysin group and 10.3% in the placebo group. We calculated the risk ratio for the outcome total number of adverse events: RR 1.62, 95% CI 0.69 to 3.82 (Fig. 2, Table 3). The trialists reported only one serious non-fatal adverse event in the placebo group: Haematemesis. They did not report on any adverse effects specifically associated with cerebrolysin, for example, hypersensitivity reactions.

4.3.2. Sensitivity analyses

As we only included one study, we did not perform the planned sensitivity analyses.

5. Discussion

The only included trial, supported by the manufacturer of cerebrolysin, EBEWE Pharma, did not provide sufficient evidence of the effects of cerebrolysin on clinically relevant outcome measures for acute ischaemic stroke. In terms of all-cause death, cerebrolysin performed no better than placebo. Despite the lack of evidence of efficacy in acute ischaemic stroke cerebrolysin is widely used in Russia and China. The methodological quality of clinical trials of cerebrolysin was not sufficient for inclusion in this review. It is worth mentioning that among the excluded studies, the Skvortsova 2004 trial [63] of cerebrolysin 10 ml and 50 ml versus placebo for 10 days reported no difference in the all-cause death between cerebrolysin and placebo by day 30 after stroke onset. Therefore, the routine use of cerebrolysin in patients with acute ischaemic stroke is not supported by any evidence from the existing clinical trials. Any further studies conducted in this area must be well-designed RCTs assessing clinical outcome measures rather than stroke scale parameters or other surrogate outcomes such as infarct volume. The studies should be reported in full to allow the wider scientific community to gain a better understanding of the potential value of cerebrolysin in acute ischaemic stroke. The potential benefit of neuroprotection for clinical outcomes in acute ischaemic stroke needs to be re-assessed.

6. Authors' conclusions

6.1. Implications for practice

The only randomised controlled trial (RCT) that evaluated cerebrolysin for treating acute ischaemic stroke was not designed to enable assessment of clinical outcome measures of efficacy and, thus, does

not support the potential clinical benefits of this intervention. The use of cerebrolysin is not supported by reliable evidence. Based on this trial, the routine administration of cerebrolysin to patients with acute ischaemic stroke is not recommended until its effects are tested in larger RCTs.

6.2. Implications for research

Future research, if any, needs to focus on well-designed RCTs to assess the potential benefits of cerebrolysin for acute ischaemic stroke. The trialists must ensure that they use pragmatic clinical outcome measures, including as a minimum, early death, dependency, all-cause death and adverse events. The trialists must provide a detailed description of any basic or routine therapy used concurrently with cerebrolysin (these should be the same in both the intervention and control groups). The trials should be reported in full and preferably conform to the Consolidated Standards of Reporting Trials (CONSORT) statement [43].

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Contributions of authors

Lilia Ziganshina prepared the protocol. Tatyana Abakumovs and Alexandra Kuchaeva performed literature searches of the Russian language studies. Lilia Ziganshina, Alexandra Kuchaeva and Tatyana Abakumova assessed citations, abstracts and full texts of trial reports for eligibility, and extracted data. Lilia Ziganshina drafted the text of the review.

Declarations of interest

None known.

Sources of support

Internal sources

- Kazan State Medical Academy, Russian Federation.
- Cochrane Stroke Group, UK.
- Liverpool School of Tropical Medicine, UK.

External sources

- No sources of external support supplied

Appendix 1.

MEDLINE search strategy

We used the following search strategy based on a combination of controlled vocabulary (/) and free text terms (.tw) for MEDLINE (Ovid), and modified it for the other databases.

1. cerebrovascular disorders/or basal ganglia cerebrovascular disease/or exp brain ischemia/or carotid artery diseases/or carotid artery thrombosis/or cerebrovascular accident/or exp brain infarction/or exp hypoxia-ischemia, brain/or intracranial arterial diseases/or cerebral arterial diseases/or exp "intracranial embolism and thrombosis".
2. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
3. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
4. 1 or 2 or 3.
5. (cerebrolysin$ or CERE or FPF-1070 or FPF1070 or cortexin$ or CORT or N-PEP-12).tw
6. 4 and 5.
7. limit 6 to humans.

References

[1] AHA, American Heart Association, Heart and Stroke Disease Statistics, 2007, Available at http://www.americanheart.org/presenter.jhtml? (accessed April 2007).

[2] X.A. Alvarez, V.R. Lombardi, L. Corzo, P. Perez, V. Pichel, M. Laredo, et al., Oral cerebrolysin enhances brain alpha activity and improves cognitive performance in elderly control subjects, *Journal of Neural Transmission* **59**(Suppl) (2000), 315–328.

[3] K. Asplund, Haemodilution for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (4) (2002), [Art. No.: CD000103. DOI:10.1002/14651858.CD000103].

[4] P.M.W. Bath, Prostacyclin and analogues for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (3) (2004), [Art. No.: CD000177.pub2. DOI:10.1002/14651858.CD000177.pub2].

[5] P.M.W. Bath, Theophylline, aminophylline, caffeine and analogues for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (3) (2004), [Art. No.: CD000211.pub2. DOI:10.1002/14651858.CD000211.pub2].

[6] P.M.W. Bath and F.J. Bath-Hextall, Pentoxifylline, propentofylline and pentifylline for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (3) (2004), [Art. No.: CD000162.pub2. DOI: 10.1002/14651858.CD000162.pub2].

[7] P.M.W. Bath, M. Willmot, J. Leonardi-Bee and F.J. Bath-Hextall, Nitric oxide donors (nitrates), L-arginine, or nitric oxide synthase inhibitors for acute stroke, *Cochrane Database of Systematic Reviews* (4) (2002), [Art. No.: CD000398. DOI: 10.1002/14651858.CD000398].

[8] D. Bereczki and I. Fekete, Vinpocetine for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (4) (1997), [Art. No.: CD000480. DOI: 10.1002/14651858.CD000480].

[9] D. Bereczki, I. Fekete, G.F. Prado and M. Liu, Mannitol for acute stroke, *Cochrane Database of Systematic Reviews* (3) (2007), [Art. No.: CD001153. DOI: 10.1002/14651858.CD001153.pub2].

[10] E. Berge and P. Sandercock, Anticoagulants versus antiplatelet agents for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (4) (2002), [Art. No.: CD003242. DOI: 10.1002/14651858.CD003242].

[11] Blood Pressure in Acute Stroke Collaboration (BASC), Vasoactive drugs for acute stroke, *Cochrane Database of Systematic Reviews* (4) (2000), [Art. No.: CD002839. DOI: 10.1002/14651858.CD002839].

[12] Blood Pressure in Acute Stroke Collaboration (BASC), Interventions for deliberately altering blood pressure in acute stroke, *Cochrane Database of Systematic Reviews* (3) (2001), [Art.No.: CD000039. DOI: 10.1002/14651858.CD000039].

[13] R. Bonita, Epidemiology of stroke, *Lancet* **339** (1992), 342–344.

[14] R. Bonita, A. Stewart and R. Beaglehole, International trends in stroke mortality: 1970–1985, *Stroke* **21** (1990), 989–992.

[15] L. Candelise and A. Ciccone, Gangliosides for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (4) (2001), [Art. No.: CD000094. DOI: 10.1002/14651858.CD000094].
[16] E.L. Chukanova, The effect of cerebrolysin on the clinical symptoms and the course of ischemic encephalopathy, *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* **105**(1) (2005), 42–45.
[17] A. Ciccone and I. Santilli, Glycoprotein IIb-IIIa inhibitors for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (4) (2006), [Art. No.: CD005208. DOI: 10.1002/14651858.CD005208.pub2].
[18] B. Cuparnecu, Efficacy of cerebrolysin in patients with ischaemic stroke of the middle cerebral artery, *Pharmacology and Toxicology* **89**(Suppl 1) (2001), 136.
[19] European Ad Hoc Consensus Group, Neuroprotection as initial therapy in acute stroke, Third report of an Ad Hoc Consensus Group Meeting, *Cerebrovascular Diseases* **8** (1998), 59–72.
[20] Y. Fragoso and D.C. Dantas, Cerebrolysin for Alzheimer's disease, *Cochrane Database of Systematic Reviews* (3) (2002), [Art. No.: CD003801. DOI: 10.1002/14651858.CD003801].
[21] B. French, A. Forster, P. Langhorne, M.J. Leathley, J. McAdam, C.I.M. Price, et al., Repetitive task training for improving functional ability after stroke, *Cochrane Database of Systematic Reviews* (3) (2006), [Art. No.: CD006073. DOI: 10.1002/14651858.CD006073].
[22] B.G. Gafurov and N.A. Alikulova, Clinical and pathogenetical peculiarities and treatment policy in ischemic stroke of elderly and old age, *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* **104**(Suppl 11) (2004), 44–46.
[23] C. Gandolfo, P. Sandercock and M. Conti, Lubeluzole for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (1) (2002), [Art. No.: CD001924. DOI: 10.1002/14651858.CD001924].
[24] O.A. Gromova, V.E. Tret'iakov, S.A. Moshkovskii, E.I. Gusev, A.A. Nikonov, L.A. Val'kova, et al., An oligopeptide membrane fraction of cerebrolysin, *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* **106**(7) (2006), 68–70.
[25] G. Gubitz, P. Sandercock and C. Counsell, Anticoagulants for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (3) (2004), [Art. No.: CD000024.pub2. DOI: 10.1002/14651858.CD000024.pub2].
[26] E.I. Gusev, V.I. Skvortsova and L.V. Stakhovskaia, Epidemiology of stroke in Russia, *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* **8** (2003), 4–9.
[27] Z. Haffner, Cerebrolysin in acute ischemic stroke, Stroke Trials Directory, Internet Stroke Center, 2001, Available at www.strokecenter.org/trials/
[28] Z. Haffner, R. Gmeinbauer and H. Moessler, A randomized, doubleblind, placebo-controlled trial with cerebrolysin in acute ischaemic stroke, *Cerebrovascular Diseases* **11**(Suppl 4) (2001), 76.
[29] Z. Hong, X.W. Li, Q.T. Chen, B.Z. Zhang and B.H. Su, Re-evaluation of cerebrolysin in treatment of early rehabilitation after ischemic stroke, *Chinese Journal of New Drugs and Clinical Remedies/Zhongguo Xinyao Yu Linchuang Zaz* **21**(3) (2002), 133–136.
[30] Z. Hong, G. Zhu and H. Chen, The clinical efficacy of cerebrolysin in the treatment of acute ischemic stroke, *Chinese Journal of Geriatric Heart Brain and Vessel Diseases* **7**(5) (2005), 331–333.
[31] J. Horn and M. Limburg, Calcium antagonists for acute ischemic stroke, *Cochrane Database of Systematic Reviews* (1) (2000), [Art. No.: CD001928. DOI: 10.1002/14651858.CD001928].
[32] J.B. Jin, Efficacy of treating cerebral apoplexy with xingnaojing compared with cerebrolysin, a report of 96 cases, *Clinical Medicine/Lin chuang yi xue* **19**(9) (1999), 53–54.
[33] A.E. Kulchikov and A.N. Makarenko, Neuroimmunocorrective activity is a future for neuroprotective agent cerebrolysin, *International Journal of Stroke* **3**(Suppl 1) (2008), 324–325.
[34] A.E. Kulchikov and A.N. Makarenko, The use of neuropeptides as neuroimmunocorrection agents in stroke induced viral complications, *International Journal of Stroke* **3**(Suppl 1) (2008), 456.
[35] G. Ladurner, R. Gmeinbauer and H. Moessler, Cerebrolysin in acute ischaemic stroke: A randomized, placebo-controlled trial with a neuroprotective agent, *Cerebrovascular Diseases* **11** (2001), 75.
[36] G. Ladurner, P. Kalvach and H. Moessler, The Cerebrolysin Study Group, Neuroprotective treatment with cerebrolysin in patients with acute stroke: A randomised controlled trial, *Journal of Neural Transmission* **112** (2005), 415–428.
[37] G. Ladurner, Neuroprotection in acute ischaemic stroke, *Stroke* **32** (2001), 323.
[38] J. Leonardi-Bee, T. Steiner and F. Bath-Hextall, Naftidrofuryl for acute stroke, *Cochrane Database of Systematic Reviews* (2) (2007), [Art.No.: CD005478. DOI: 10.1002/14651858.CD005478.pub2].
[39] M. Liu, C. Counsell, X.L. Zhao and J. Wardlaw, Fibrinogen depleting agents for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (3) (2003), [Art. No.: CD000091. DOI: 10.1002/14651858.CD000091].

[40] A.N. Makarenko, N.S. Kositsin, I.V. Nazimov, M.M. Svinov, E.V. Goloborod'ko and N.V. Pasikova, A comparative study of antistroke activity of the new drug "cerebral" and its fractions in rats, *Eksperimental'naia i Klinicheskaia Farmakologiia* **68**(2) (2005), 15–20.
[41] A.N. Makarenko and A.E. Kulchikov, Treatment of infection complications of the acute stroke by cerebrolysin, *International Journal of Stroke* **1**(Suppl 1) (2006), 81.
[42] M. Mielke, J. Wardlaw and M. Liu, Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (4) (2004), [Art. No.: CD000514.pub2. DOI: 10.1002/14651858.CD000514.pub2].
[43] D. Moher, K.F. Schulz and D.G. Altman, The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomised trials, *Lancet* **357** (2001), 1191–1194.
[44] K.W. Muir and K.R. Lees, Excitatory amino acid antagonists for acute stroke, *Cochrane Database of Systematic Reviews* (3) (2003), [Art.No.: CD001244. DOI: 10.1002/14651858.CD001244].
[45] Nordic Cochrane Centre, The Cochrane Collaboration, Review Manager (RevMan). 5.0, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2008.
[46] L.S. Onishchenko, O.N. Gaikova and S.N. Ianishevskii, Changes in the focus of experimental ischemic stroke under the influence of neuroprotective drugs, *Morfologiia* **130**(6) (2006), 40–46.
[47] N. Qizilbash, S.L. Lewington and J.M. Lopez-Arrieta, Corticosteroids for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (3) (2002), [Art. No.: CD000064. DOI: 10.1002/14651858.CD000064].
[48] J. Ren, Z. Qiu, Z. Du and L. Fan, Effect comparison of injection disodium cytidine triphosphate and cerebrolysin in treatment of acute cerebral vascular disease, *China Pharmacist* **5**(1) (2002), 45–46.
[49] S. Ricci, M.G. Celani, A.T. Cantisani and E. Righetti, Piracetam for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (2) (2006), [Art. No.: CD000419.pub2. DOI: 10.1002/14651858.CD000419.pub2].
[50] E. Righetti, M.G. Celani, T. Cantisani, R. Sterzi, G. Boysen and S. Ricci, Glycerol for acute stroke, *Cochrane Database of Systematic Reviews* (2) (2004), [Art. No.: CD000096.pub2. DOI: 10.1002/14651858.CD000096.pub2].
[51] C. Riley, B. Hutter-Paier, M. Windisch, E. Doppler, H. Moessler and R. Wronski, A peptide preparation protects cells in organotypic brain slices against cell death after glutamate intoxication, *Journal of Neural Transmission* **113**(1) (2006), 103–110.
[52] D.R. Sagatov, Use of emoxepin in the treatment of ischemic stroke in young adult patients, *International Journal of Stroke* **3**(Suppl 1) (2008), 123.
[53] P.A.G. Sandercock, C. Counsell, G.J. Gubitz and M.C. Tseng, Antiplatelet therapy for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (3) (2008), [Art. No.: CD000029. DOI: 10.1002/14651858.CD000029.pub2].
[54] P. Sandercock, C. Counsell and M.C. Tseng, Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin foracute ischaemic stroke, *Cochrane Database of Systematic Reviews* (3) (2008), [Art. No.: CD000119. DOI: 10.1002/14651858.CD000119.pub3].
[55] N.S. Sapronov, V.V. Bul'on, N.N. Kuznetsova and E.N. Selina, The neuroprotector effect of a new taurine derivative on a model of compression spinal cord trauma in rats, *Eksperimental'naia i Klinicheskaia Farmakologiia* **68**(6) (2005), 45–48.
[56] E. Schauer, R. Wronski, J. Patockova, H. Moessler, E. Doppler, B. Hutter-Paier, et al., Neuroprotection of cerebrolysin in tissue culture models of brain ischemia: Post lesion application indicates a wide therapeutic window, *Journal of Neural Transmission* **113**(7) (2006), 855–868.
[57] N.A. Shamalov, L.V. Stakhovskaya, L.V. Gubsky, I.V. Tikhonova, A.S. Smichkov, V.I. Skvortsova, et al., Effects of the neuroprotective drug cerebrolysin on the infarct volume after acute ischemic stroke, *Cerebrovascular Diseases* **19**(Suppl 2) (2005), 107.
[58] Y.-M. Shi, Cerebrolysin in acute cerebral hemorrhage, *Chinese Journal of Nervous and Mental Diseases* **16**(4) (1990), 228–230.
[59] A. Shuaib, K.R. Lees, P. Lyden, J. Grotta, A. Davalos, S.M. Davis, et al., NXY-059 for the treatment of acute ischemic stroke, *New England Journal of Medicine* **357**(6) (2007), 562–571.
[60] V.I. Skvortsova, N.A. Shamalov, H. Moessler and P.H. Novak, Beneficial effects of the neurotrophic drug cerebrolysin on the infarct volume after acute stroke, *Cerebrovascular Diseases* **25**(Suppl 2) (2008), 145.
[61] V.I. Skvortsova, N.A. Shamalov, H. Moessler and P.H. Novak, Positive impacts of the neurotrophic drug cerebrolysin on the infarct volume after acute stroke, *International Journal of Stroke* **3**(Suppl 1) (2008), 137.
[62] V.I. Skvortsova, N.A. Shamalov, L.V. Stakhovskaya, L.V. Gubsky, I.V. Tikhonova and A.S. Smichkov, Cerebrolysin in acute ischaemic stroke: Results of randomised, double blind, placebo-controlled study, *Cerebrovascular Diseases* **19**(Suppl 2) (2005), 76.

[63] V.I. Skvortsova, L.V. Stakhovskaya, L.V. Gubsky, N.A. Shamalov, I.V. Tikhonova and A.S. Smychkov, A randomised, double-blind, placebo-controlled study of cerebrolysin safety and efficacy in the treatment of acute ischaemic stroke, *Zhurnal Nevrologii I Psikhiatrii Imeni S.S. Korsakova* **0**(11) (2004), 51–55.
[64] Tirilazad International Steering Committee, Tirilazad for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (4) (2001), [Art. No.: CD002087. DOI: 10.1002/14651858.CD002087].
[65] B.S. Vilenskii and N.N. Iakhno, The problem of cerebral stroke: Its contemporary state, *Vestnik Rossiiskoi Akademii Meditsinskikh Nauk* **9–10** (2006), 18–24.
[66] B.S. Vilensky, M.M. Odinak, E.A. Shirokov, I.A. Voznuk, G.M. Semenova and T.B. Grinevich, Experience with endolumbar application of cerebrolysin in hemispheric ischemic stroke, *Zhurnal Nevrologii I Psikhiatrii Imeni S.S. Korsakova* **100**(11) (2000), 31–34.
[67] B. Vilensky, O. Vinogradov, A. Kuznetsov, S. Zimmermann-Meinzingen and O. Soloviev, Favorable influence of repeat cerebrolysin application in stroke patient rehabilitation, *International Journal of Stroke* **1**(Suppl 1) (2006), 170.
[68] N.G. Wahlgren and N. Ahmed, Neuroprotection in cerebral ischaemia: Facts and fancies – the need for new approaches, *CerebrovascularDiseases* **17**(Suppl 1) (2004), 153–166.
[69] H.T. Wang, The analysis of the efficacy of insulin, cerebrolysin, nitrendipine in the treatment of cerebral infarction. *Practical Geriatrics* **11** (1997), 135–136.
[70] J.M. Wardlaw, V. Murray, E. Berge and G.J. del Zoppo, Thrombolysis for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (4) (2009), [Art. No.: CD000213. DOI: 10.1002/14651858.CD000213.pub2].
[71] World Health Organization, The Atlas of Heart Disease and Stroke, Available at http://www.who.int/cardiovascular_diseases/resources/atlas/en/ (accessed April 2007).
[72] G.K. Wong, X.L. Zhu and W.S. Poon, Beneficial effect of cerebrolysin on moderate and severe head injury patients: Result of a cohort study, *Acta Neurochirurgica Supplement* **95** (2005), 59–60.
[73] X. Wu, Urokinase therapy in acute ischemic stroke, Proceedings of the 4th Chinese Stroke Conference, China, Chengdu, 1995, pp. 149–150.
[74] V.A. Yavorskaya and O.B. Bondar, Clinical features of cerebrolysinum application in patients in acute period of ischemic stroke, *International Journal of Stroke* **3**(Suppl 1) (2008), 141.
[75] S.H. Zhang and X.M. Lu, Nursing care of the patient with cerebral infarction and aphasia receiving carotid internal drug injection and early speech training, *Journal of Nursing Science* **12**(1) (1997), 34–35.
[76] Q.Y. Zhang, J. Xiong and R. Wang, Study on the effectiveness of cerebrolysin in 27 patients with cerebral infarction, *Chinese Journal of Pharmacoepidemiology* **3**(4) (1994), 181–182.
[77] X. Zeng, M. Liu, Y. Yang, Y. Li and K. Asplund, Ginkgo biloba for acute ischaemic stroke, *Cochrane Database of Systematic Reviews* (4) (2005), [Art. No.: CD003691.pub2. DOI: 10.1002/14651858.CD003691.pub2].
[78] G.-X. Zhu, Z. Hong, J.-L. Yao and L.-Y. Yu, Double-blind and randomised placebo-controlled trial of cerebrolysin in improvement of nerve function and living ability in patients with ischemic stroke, *Chinese Journal of Clinical Rehabilitation* **7**(22) (2003), 3084–3085.

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Psychiatric drugs as agents of trauma

Charles L. Whitfield*
Private Practice of Trauma Psychology, Psychiatry, and Addiction Medicine
Consultant and Research Collaborator at the Centers for Disease Control and Prevention, Atlanta, GA, USA
Board of Directors of the Leadership Council on Child Abuse & Interpersonal Violence, Baltimore, MD, USA

Abstract. Drawing on the work of numerous psychiatrists and psychopharmacologists and my own observations, I describe how most common psychiatric drugs are not only toxic but can be chronically traumatic, which I define in some detail throughout this paper. In addition to observing this occurrence among numerous of my patients over the past 20 years, I surveyed 9 mental health clinicians who had taken antidepressant drugs long-term. Of these 9, 7 (77%) experienced bothersome toxic drug effects and 2 (22%) had become clearly worse than they were before they had started the drugs. Based on others' and my observations I describe the genesis of this worsened condition which I call the *Drug Stress Trauma Syndrome*.

These drug effects can be and are often so detrimental to the quality of life among a distinct but significant minority of patients that they can no longer be considered trivial or unimportant. Instead, they are so disruptive to many patients' quality of life that their effect becomes traumatic, and are thereby agents of trauma. These observations and preliminary data may encourage others to look into this matter in more depth.

1. Introduction

Depending on how we look at it, trauma can be simple, complex, or somewhere in between. In its simpler form it is any serious injury to the body, often resulting from an accident or violence and sometimes from a drug or medical procedure. Beyond the body, psychological trauma often results from an event that causes great distress or an emotional wound leading to psychological injury [18, 28, 52], and which may also result from a drug or medical procedure. Psychological trauma often accompanies physical trauma. Trauma can result from natural disasters such as earthquakes, fires, floods, hurricanes and severe storms that often cause death, injury, and property damage. These are usually single events that involve fewer of the confounding and complicating variables present in so many other kinds such as combat trauma and child maltreatment and neglect, including physical, sexual, or emotional abuse, bullying, domestic violence, or the witnessing of any of these [12, 13, 39–41, 49].

Any of these traumas may lead to one of the three main variants of posttraumatic stress disorder (PTSD) [11, 45, 50], including classical, complex and sub-variant PTSD, summarized in Table 1. In this article I add a fourth kind by describing how psychiatric drugs can act as traumatizing agents and make patients worse, which I call the Drug Stress Trauma Syndrome (DSTS), described below. After taking one, and usually more psychiatric drugs over time, many people end up feeling more distressed. They may experience a worse quality of life than they did before they started taking the drugs [6, 7, 21, 25, 26,

*Address for correspondence: Charles L. Whitfield, MD, 3462 Hallcrest Dr., Atlanta, GA 30319-1910, USA. Tel.: +1 404 843 3585; E-mail: c-bwhit@mindspring.com.

Table 1
Variants of PTSD

PTSD variant	Characteristics and description
PTSD Sub-variant	Little or no memory of trauma experiences or history. Often fulfill less *DSM* diagnostic criteria than required for classical PTSD, yet patient usually has one or more trauma spectrum disorders and other trauma effects.
Classical PTSD	Memory/awareness for enough trauma effects to fulfill *DSM* criteria for PTSD categories A – F
Complex PTSD	Extreme variant after repeated severe trauma, especially during childhood. Commonly experience increased *dissociation*, marked *relationship difficulties, re-victimization, somatization*, extreme *disrupted feelings* and *emotions,* and a *lost sense of self* and *meaning.*
Drug Stress Trauma Syndrome (DSTS)	An unknown minority % may have DSTS without having another PTSD variant. Needs data gathering. Many usually have another variant of PTSD *plus* DSTS.

33, 35, 46, 47, 49–51]. First, it will be useful to describe and contrast the drugs in context with common illegal drugs according to their risk and toxicity.

2. Illegal drug toxicity

Illegal drugs often have toxic effects on our body and mind [24, 31, 38]. There are also legal *system* consequences for simple possession and use in most countries. Having worked in the field of addiction medicine since 1974 and psychiatry since 1980, I rank *illegal* drugs in order of the *most toxic* and dangerous: 1) phencyclidine (PCP, "Angel Dust") is number one. In decreasing order of toxicity, I rank 2) amphetamines, including methamphetamine, as second. Then 3) cocaine, another stimulant, and not much different than amphetamines, but with a detrimentally short half-life. Fourth, is 4) heroin, a painkiller like morphine and the other opiates – all with several toxic effects. Next are 5) psychedelic drugs (erroneously called "hallucinogens"). And finally, 6) cannabis (marijuana) is probably the most used illegal drug today, with the toxic effects of over-sedation or "dumbing down" (which most *legal* and illegal psychoactive drugs also commonly cause), lung irritation and damage, dependence/addiction and withdrawal symptoms. Like *all these drugs* their *illegality, way of use* (ingesting, snorting, smoking or injecting), and *lifestyle* add more to their toxicity.

As toxic as these six kinds of drugs are, and not to discount their dangers, to keep it in perspective, in the USA the *legal* drugs alcohol and nicotine *disable* and *kill 25 times more* people (about 500,000 yearly deaths) than all of these illegal drugs *combined* [36].

3. Legal drug toxicity: How might psychiatric drugs make you worse?

Just because a drug may be legal, i.e., approved by the FDA or the equivalent worldwide and readily available from the medical and psychiatric system (physicians, nurses, pharmacists and the like) does not make them any less toxic than the illegal drugs listed above. In fact, some of the legal psych drugs are as or *more* toxic [1, 6, 7, 26, 33–35, 44, 49–51]. Psychiatrist and psycho-pharmacologist Peter Breggin wrote in 2008 [6, 7], "People commonly use alcohol, marijuana and other non-prescription drugs to dull their feelings. Usually they do not fool themselves into believing they are somehow improving the function of their minds and brains. Yet when people take psychiatric drugs, they almost always do so

without realizing that the drugs 'work' by *disrupting brain function*, that the drugs cause withdrawal effects, and that they frequently result in dangerous and destructive mental reactions and behaviors" (my italics).

In 1999 describing the course of events following *chronic psychoactive drug-taking* Hollister reviewed Shuster's classic 1961 formulation [23, 42]: 1) the drug perturbs the normal homeostasis of an organ system by virtue of effects on enzymes, neurotransmitters, receptors or second messengers. 2) To compensate, the body responds by increasing the amounts of each. When this occurs the patient may become tolerant to the drug. 3) To maintain the desired effects of the drug, the dose is increased to overcome the body's compensatory reactions. However, increasing doses result in renewed attempts at compensation. 4) Several cycles of this sort may ensue. 5) When a drug is withdrawn, the overcompensated mechanisms are now unopposed, resulting in a withdrawal reaction, generally characterized by symptoms and signs opposite to those usually produced by the drug (physical dependence) [23, 42].

Hollister wrote: "This schema was first introduced to explain the sequence of drug-taking of drugs of abuse, which also involve 'psychic [psychological/neurological] dependence'. However, it may be extended to a variety of drugs... It has been long recognized that withdrawal syndromes vary among classes of drug. It 1964, the World Health Organization classified withdrawal syndromes in that fashion: Barbiturate-alcohol type, opiate type and stimulant type. *This classification* still applies and *might* be modified now to *include* other drugs not usually abused, but which alter central nervous system function, such as *antidepressants* and *antipsychotics*, where discontinuation syndromes were unanticipated and more subtle and psychic dependence was not [suspected to be] present. We may conclude that any drug which disturbs normal physiology, biochemistry or gene expression may set the stage for such a reaction" (my italics) [23].

Also in 1999 psychiatrist and psycho-pharmacologist David Healy and Richard Tranter described reactions to taking psychiatric drugs, including their withdrawal, as *pharmacological stress diathesis syndromes* [22]. They said, "Recent descriptions of discontinuation syndromes following treatment with antidepressants and antipsychotics, in some cases long lasting, challenge both public and scientific models of addiction and drug dependence. Antipsychotic and antidepressant drug dependencies point to a need to identify predisposing constitutional and personality factors in the patient, pharmacological *risk factors in the drug* and aspects of *therapeutic style* that may contribute to the development of *stress syndromes*. The stress syndromes following antipsychotics also point to the *probable* existence of a *range of syndromes* emerging within treatment. The characteristics of these need to be established" (my italics). Similarly, psycho-pharmacologist Ross Baldessarini and AC Vignera have called these psychiatric drug effects *pharmacologic stress, iatrogenic pharmacologic stress,* and *drug discontinuation-associated stress* [2, 3, 4].

Ranking the psych drugs in decreasing order as I did above for the illegal drugs, first are 1) the antipsychotic drugs, which are generally so disabling and toxic that they have been shown to cause early death [6, 7, 46, 47]. Second are 2) the antidepressant drugs, which share many toxic effects with the antipsychotics and often *cause* an increase in suicidal thoughts and completed suicides, as well as homicides, when compared with placebos [6, 7, 19]. Next are 3) the stimulants of the methylphenidate (Ritalin) and amphetamine type (which are nearly all amphetamines of one sort or another). Then 4) the benzodiazepine sedatives ("benzos") whose main toxicities are over-sedation and emotional numbness (similar to the antipsychotics and antidepressants) and probably having the most painful withdrawal syndrome of all legal and illegal drugs for most people. Next, 5) the anti-convulsants, cleverly called "mood stabilizers" for marketing purposes, although they have little to do with mood and they commonly cause numerous toxic effects and an often painful withdrawal [6, 34]. I summarize major risks and

Table 2
Some characteristics of illegal and legal psychoactive drugs

Illegal drugs
- Overdose from toxic effects on body & mind
- Organ damage from chronic use
- "Dumbing-down" effect on mental & social function & self esteem
- Legal system consequences
- Most-toxic-drug rank: Phencyclidine (PCP), amphetamines, cocaine, heroin, psychedelics, cannabis
- The legal drugs alcohol & nicotine disable & kill 25X more people than *all these* illegal drugs *combined*

Legal drugs – have similar and often more toxic effects
- Organ damage from chronic use (e.g., as obesity, diabetes; fetal & brain/nerve damage, dementia, depression, anxiety, tremor)
- "Dumbing-down" effect on mental & social function & self esteem
- Forced drugging by hospital, court & state system
- Withdrawal common & bothersome; often harmful to self & others; usually *misdiagnosed*
- Akathisia ± withdrawal akathisia → suicide & homicide
- Violence is common with both legal & illegal psych drugs
- "Mental illness" labeling → fear & shame, discrimination, isolation

toxicities of both the illegal and legal psychoactive drugs in Table 2. Here follows a selection of references for a more detailed summary of these drug effects [6, 8, 19, 20, 26, 33, 46–51].

4. Drug Stress Trauma Syndrome

I have seen countless patients over the past 20 years who came to me currently taking – or having taken in the past – from five to twenty psych drugs, none of which had helped them significantly long-term with their original complaints. Many of these people had gotten worse. I began to notice a pattern wherein a vicious cycle unfolded among a distinct minority of them. I observed that taking many of these drugs was often unpleasant, usually did not work well, and had become detrimental to their mental, relationship and behavioral health. They were worse than they were before they started the drugs. Here is how I have seen the Drug Stress Trauma Syndrome usually to come about.

5. Genesis of DSTS

The person enters the health care system with one or more psychological or psychiatric symptoms or signs, from bothersome fear, anxiety, to sadness, low energy, to a behavior or relationship problem, or the like. The intake clinician usually does not carefully look for the three most common causes of these symptoms – a recent significant loss, a history of repeated trauma/PTSD and alcohol or other drug dependence. Instead, after a brief (influenced by health insurance or government treatment time limitations) and a cursory evaluation (influenced by the clinician's training and skills), and usually with no physical or laboratory examination, a psychiatric diagnosis is made. This diagnosis may be in error, such as "depression", an "anxiety disorder", "bipolar disorder", "ADHD", a "psychosis", or the like [27, 54]. Zur et al. argued: The DSM is more a political document than a scientific one. Decisions

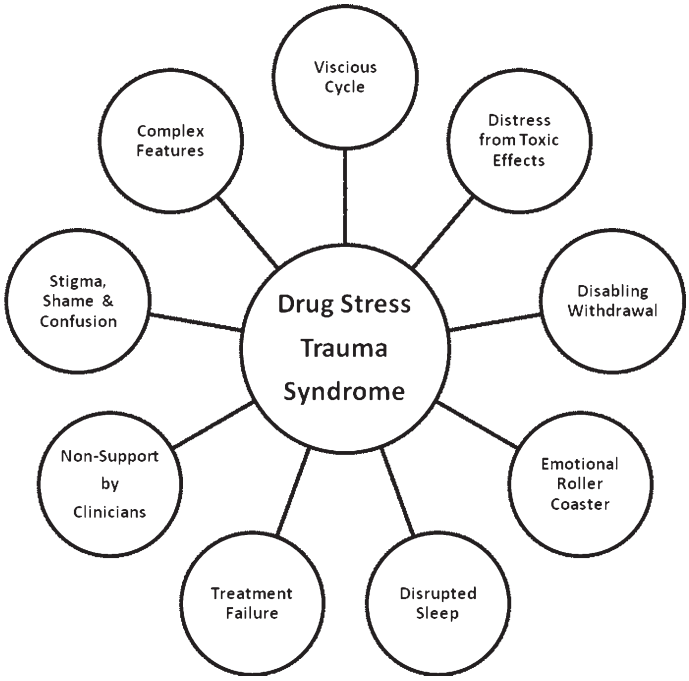

Fig. 1. Drug Stress Trauma Syndrome components.

regarding inclusion or exclusion of disorders are made by majority vote rather than by indisputable scientific data.

But it satisfies several key people: The health insurance or other authorities' requirements, the clinician, the drug industry, and/or any number of authority figures (boss, court, probation officer, teachers or other school administration, parents or other family members) and, at least temporarily, the patient.

Not addressing that the patient's symptoms and/or signs may instead be grief-related [43, 49], trauma effects [18, 28] or due to an alcohol or other drug problem [31, 38, 50], a shortcut of one or more psychiatric drugs is prescribed. The clinician usually gives the patient little or no warning about drug toxicity or drug withdrawal [15], and offers them no counseling or psychotherapy (which would likely have been more appropriate) [6, 7]. Perhaps unknowingly acting in their favor long term, up to 25% of patients do not get the prescription filled. But for those who start taking the drug(s), the first toxic effect of "medication spellbinding", chemical dissociation or numbing occurs, even though the patient may not be fully aware of it [6]. An unaware observer – trying to be objective – may conclude something like, "So far, so good".

Sooner or later, the patient either stops taking or forgets to take the drug, and for most psychiatric drugs, one of the most common toxic effects begins to occur – drug *withdrawal symptoms*. If the withdrawal symptoms are bothersome enough, the patient usually contacts their prescribing clinician or physician who should – but usually does not – recognize them as being in drug withdrawal. Instead, they tend to misinterpret the symptoms as a re-emergence or worsening of the patient's original possible misdiagnosis' symptoms or signs [53]. With this misinterpretation, or second misdiagnosis, they commonly then prescribe a higher drug dose, or a different or stronger drug. They usually give the patient no education or insight on withdrawal symptoms, and again, no serious yet appropriate psychotherapy or counseling [6, 7, 33, 48–51].

Table 3
Drug Stress Trauma Syndrome (DSTS) Genesis by stages of system-induced psychiatric/psychological illness

Actions	Dynamics
First "Diagnosis"	• With no PTSD or Alc & Drug (Chemical Dependence) assessment, wrong diagnosis is made. e.g., "Depression", "Anxiety Disorder", "Bipolar Disorder", "psychosis", "ADHD", etc.
First "Treatment"	• Not addressing trauma or A&D effects • Psychiatric drug(s) are then given inappropriately • No warning to patient of toxicity, incl. drug withdrawal • No psychotherapy or counseling → "Medication spellbinding" *
Patient eventually *stops or forgets* to take drug(s)	
Withdrawal not diagnosed	• Misinterpret drug withdrawal symptoms/effects as • "Re-emergence/worsening" of original misdiagnosed symptoms or signs (see tables) or as • Another psychiatric disorder
Withdrawal mistreated	• Mis-prescribes • Higher drug dose or • Different or stronger drug
Deterioration	• No education on withdrawal symptoms • No psychotherapy or counseling → *The Vicious Cycle* Continues • Person becomes progressively more dysfunctional ± Physically ill, hospitalizations, arrests, family dysfunction/breaks, increased medical costs & DSTS

* Medication Spellbinding = the capacity of psychoactive drugs to blunt the patient's appreciation of drug-induced mental dysfunction and, at times, to encourage a misperception that they are doing better than ever when they are actually doing worse than ever [6, 7].

The now-vicious cycle continues. Over time, the patient may become progressively more dysfunctional in their personal life, job, relationships, finances and/or with the legal system. As part of the DSTS, they often become physically ill, with one or more rushed and expensive emergency department visits, medical or psychiatric hospitalizations, violence, arrests, family dysfunction, relationship breakups, increasing medical costs and mounting debt. Eventually, similar to people with advanced alcohol or drug dependence, they may hit a "bottom".

This phenomenon, process and iatrogenically, and pharmacologically, induced condition is what I have come to call the Drug Stress Trauma Syndrome (Table 3). Using definitions of each of its four terms, I show a simpler summary that explains why I chose its terminology of DSTS in Table 4.

Table 4
Drug Stress Trauma Syndrome (DSTS) summary

Drug – most psychiatric drugs
Stress – the effects of taking & stopping the drug are not only stressful, but distressing & often disruptive to pts quality of life
Trauma – repeated distress & disruption to quality of life by the drug effects can be & often are traumatic
Syndrome – it has a recognizable pattern of symptoms & signs

For a further definition of "syndrome" wikipedia.org/wiki/Syndrome

6. How common is DSTS? Preliminary data

I don't have a reliable answer to this question. I estimate that DSTS is somewhere between rare and to a degree common. From my clinical experience, it may occur in at least a distinct minority of 20% or more of people who take psychiatric drugs long-term. We need observation, research and data-gathering for more reliable figures. For example, in April 2008 I surveyed 24 *clinicians* (social workers, nurses, therapists and counselors; 22 women and 2 men) at a one-day workshop that I gave on trauma and recovery to a total of 65 people. Of these 24 people, 9 (37.5%; 8 women and 1 man) had taken antidepressant drugs, 6 (2/3) of whom had been prescribed and taken *more than one* ADP drug. Seven of the 9 (77%) said they had felt bothersome toxic effects of the drug(s), 4 (44%) had thus far experienced a disruptive or bothersome withdrawal syndrome, and 2 (22% of the 9) said they had clearly become worse long-term than before they began taking the ADPs.

I did not ask them about their taking other psychiatric drugs. I believe that for their use of antipsychotic drugs, stimulants and benzodiazepines the percentage occurrence of DSTS may be more than 22%, and for "mood stabilizers", aka anticonvulsants, and lithium probably less. I discuss and raise several questions regarding these small and preliminary data after the next section.

7. Characteristic of DSTS

1. The first characteristic of DSTS is the *vicious cycle* described above and in Table 3. This vicious cycle contains the stressors and resulting distress described among most of the other characteristics below.
2. Distress from the *toxic effects of the drug(s).* While these are many and varied, they frequently include several of the following: Spellbinding, confusion, difficulty thinking and focusing, insomnia, metabolic – endocrine system disruption, weight gain, diabetes, easy irritability, relationship disruption, drug seeking, depression, akathisia, suicidality, various aches and pains, inability to work, and more [1, 6, 7, 21, 26, 33, 37, 44, 46–51]. These are commonly misinterpreted as being a return of the original symptoms and diagnosis.
3. *Withdrawal effects.* These withdrawal effects can be identical to the toxic effects of the drugs *and* to some of the person's original symptoms, making the differential diagnosis difficult.
4. *Emotional "roller coaster" effects.* The person may be (seemingly, on the surface) relatively peaceful, content, or numb for hours or longer, only to be followed by varying degrees of emotional and behavioral distress, sometimes markedly so. This experience will often be exaggerated by either missing a dose (usually withdrawal) or an upper-downer cycle when the person uses alternating uppers or stimulants (such as caffeine, amphetamines, or Ritalin/stimulant-type drugs to wake up, then later, sedatives to try to sleep) [26].
5. *Disrupted sleep,* which tends to lead to a painful state of chronic sleep deprivation. A stressor in itself, this sleep deprivation can then aggravate their acute and chronic stress state. This disrupted sleep is often also aggravated by the upper-downer cycle described above [26].
6. *Treatment failure.* The drug or drugs commonly do not consistently help the person's original symptoms [6, 7, 21, 25, 26, 34, 35, 37]. I have seen countless patients who came to me complaining that even after trying numerous and different psychiatric drugs, that they are either no better, or commonly that they are worse. For example, I regularly see "depressed" people who have tried a string of antidepressants [such as Prozac (fluoxetine), Paxil (paroxetine), Zoloft (sertraline), Well-

butrin (bupropion), Effexor (venlafaxine), Celexa (citalopram), Lexapro (escitalopram), Cymbalta, (duloxitine), Pristiq (desvenlafaxine)], and they are no better – or often are worse. Some of them have also been tried on the more toxic antipsychotics, also with no help, and many have additionally been prescribed anti-convulsants ("mood stabilizers"), lithium and benzodiazepines – all to little or no avail. These repeated treatment failures have contributed to their loss of hope that they can ever get better [6, 7, 22, 26, 33, 46–51].

As an example, David Healy and colleagues reported the first results of an epidemiological study in North Wales on a population that has been stable for over 100 years regarding their numbers, age, cohorts, ethnic mix and rurality. It showed that since the introduction of the modern psychiatric drugs in psychiatry that there has been a *fifteen*-fold increase in the rate of admissions to psychiatric inpatient hospitals, and a *three*-fold increase in the rate of forced psychiatric hospital admissions. It also showed that people with bipolar disorders have relapsed sooner and more often. This is a remarkable study. Overall, patients with all psychiatric conditions now appear to spend a greater amount of time in a psychiatric hospital than they would have fifty or 100 years ago. These conditions have worsened to these degrees despite the availability of supposedly effective and claimed prophylactic drug treatments. These findings are incompatible with drug treatments' being effective in practice for a majority of the patients [21].

7. Relative *non-support from* psychiatrists, other physicians and clinicians for using non-drug healing and recovery aids. Most of my patients have told me of having had this experience with other physicians, and I have seen it repeatedly over time in most dimensions of psychiatry from discussions with colleagues to psychiatry education events [5, 15, 32].
8. *Stigma, shame* and *confusion* from all of the above, including having been first labeled with a mental illness, promised improvement, and then not getting better with all these "state of the art" psych drugs that they see advertised on TV, in magazines, and elsewhere [5, 6, 7, 46, 47]. These painful feelings may aggravate the above stress responses.
9. The *presence* of DSTS then reactivates and often worsens any underlying PTSD, alcoholism, other chemical dependence, or other problems in their life. The original failure to address and treat the underlying trauma and its effects is a major factor in the genesis of PTSD. Most of the patients that I found to have the features of DSTS also had an underlying PTSD. So, rather than psychiatric drugs helping them, a fair percentage of patients with PTSD who are treated with the drugs appear to have been made worse. Instead of helping their PTSD this iatrogenic and drug-mediated worsening is likely relatively common among the multi-millions of people who are treated with psychiatric drugs today.

8. Healing from DSTS

10. *Complex features*. This painful syndrome is not usually easy to recognize and diagnose. It usually cannot be readily seen in a 5 to 15 minute medication follow-up check by a physician – which is the usual time approved by the health insurance industry, aka "managed care". If government-run medicine takes hold in the USA, it will get worse. It takes enough time to recognize the many dimensions of DSTS, which usually requires the taking of a careful and thorough initial history from the patient. Then it will likely take a number of follow-up visits and psychotherapy sessions, coordinated with a physician with expertise in treating PTSD and helping people slowly detoxify from psychiatric drugs. Many affected patients won't be able to recognize that it is the drugs that are making them worse due to their lack of knowledge and the spellbinding effects of the drugs.

For the person who has DSTS or similar symptoms, negotiating their recovery may seem like trying to walk through a mind field. They usually have to deal with multiple people: Clinicians, health insurance and payers, family (some of whom may want them to stay "mentally ill"), friends, community, and other authority figures. Navigating all these requires a self-commitment and focus on recovery, with ongoing patience and persistence. Some several thousand traumatized and damaged patients and their families have brought successful lawsuits against the drug makers, especially for drug-caused completed suicides, diabetes, birth defects and addictions [29].

Based on my long experience assisting many patients with it, to help someone heal from DSTS the clinician usually has to first realize that the patient may have it. The patient may also eventually have to self-diagnose it. The clinician then helps them gradually (over months or longer) decrease the dose of the psychiatric drugs and eventually stop taking them. If appropriate, they may also consider referring the patient to a psychotherapist or counselor who knows how to assist with trauma recovery and if indicated, alcohol and other drug dependence recovery [14, 16, 17, 30]. The patient learns to tolerate the emotional and physical pain of withdrawal from the drugs and grieving any trauma effects. They will need to get the right nutrition, attend any appropriate self-help meetings such as AA, NA, ACA, CoDA, EA, or AlAnon, all while being patient and persistent over months and sometimes years. This is similar to the recovery approach that I have outlined in my other books, including especially *My Recovery* [48]. For more details, see Chapter 15 in Breggin's *Brain Disabling Treatments in Psychiatry* [6] and Chapter 12 on Stopping Psychiatric Drugs in my book *You May Not be Mentally Ill* [51].

9. Questions and discussion

DSTS has several unknowns and questions. These include: 1) How often does it occur? 2) What is the relationship of DSTS's occurrence to the patient who has a prior history of repeated other kinds of trauma? And how might that affect its occurrence? Thus, 3) How common is DSTS among people with prior PTSD?

Figure 2 shows a 2-by-2 chart or two-dimensional model of psychiatric drug exposure and prior repeated trauma as factors in the genesis of DSTS that explores their relationship in 4 possible quadrants. As shown in both upper quadrants, the more prior repeated trauma in a patient will be more likely associated with increased symptoms and signs of mental illness as I summarize in Table 5 and in *The Truth about Depression* [49] and *The Truth about Mental Illness* [50]. Likewise, the more people with these symptoms and signs come to clinicians with them, given today's worldview about mental health, the more likely they will be prescribed psychiatric drugs. Given a premise of this article, those who get the most psychiatric drugs for the longest time will be the most likely to develop DSTS. By contrast, those in the left lower quadrant will be the least likely to develop DSTS because of their lower exposure to *both* repeated trauma and long-term psychiatric drug use. Finally, in the right lower quadrant of the figure my best medical estimation is that we will need more research and data on those in this category due to the small amount of preliminary data above.

Also 4) How does the distress and trauma of experiencing DSTS affect the PTSD after their trauma in that this may now be their *fourth* trauma? Their 1st original trauma was that which caused the PTSD. The 2nd occurred when the trauma survivor tried to tell their experience of the trauma to those they thought were supposed to be protecting them, but it was invalidated or rejected by their parents, parent figures or clinicians. The 3rd trauma was having been labeled as being "mentally ill" when instead they were grieving a significant loss, had PTSD or complex PTSD, or an active addiction. The 4th trauma is their now experiencing the distress of DSTS, including their confusion about the nature and unanswered fact that the psychiatric drugs have not only *not helped* them, but made them worse in the form of DSTS.

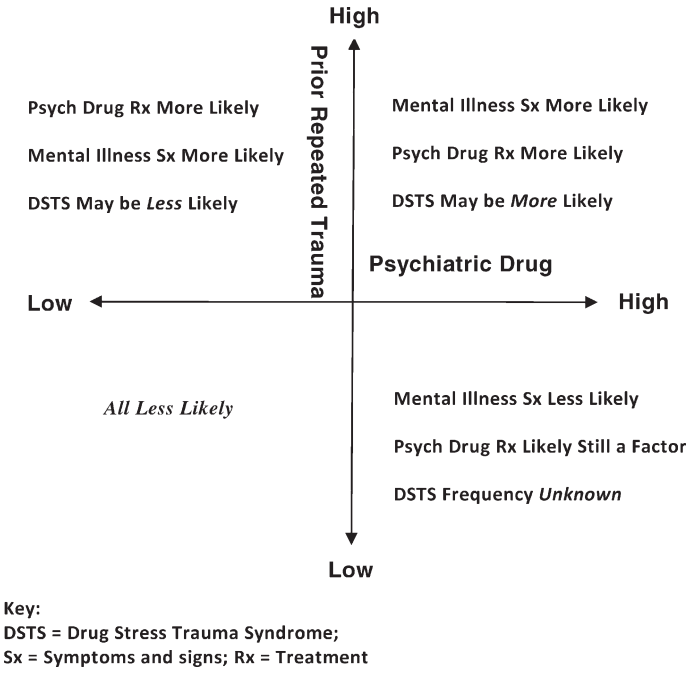

Fig. 2. Two-dimensional model of psychiatric drug exposure and prior repeated trauma as factors in genesis of DSTS.

Table 5
Number of studies that document a significant link between repeated childhood trauma and mental illness

Clinical area	Clinical	Community	Prospective	Index/Meta Analysis/LitRev	Strength of Data/Total
Depression	96	70	22	21/*	Overwhelming/327
Suicidality	22	(both)		7	Strong/29
Alcohol/Drug Probs (SA/CD)	90		21	42 Index, 11 M-A/LitRev	Powerful/153
Eating Disorders				43 Index, 7 Lit	
PTSD	54	21	10	0/6	Strong/85
Anxiety Disorder	35	38	12	15/2	Very Strong/100
Personality Disorders	35			36/1	Very Strong/76
Psychosis	67		4 (& 2 strong family studies)	37 Index 8 Lit Reviews	Very Strong/110
ADHD	15		15	4/3	Strong/77
Aggression & Violence	40		16	10	Strong/66
Low Self-Esteem	17	10	4	Only 1 of 31 didn't find it	Strong/31
Dissociative Disorders	30	16	3	11/2	Strong/57
Nicotine	10		1		Suggestive to Firm/11
Somatization	38		11	16	Strong/65
Revictimization	38		1	4	Firm to Strong/38

*Plus Bi-Polar (13), Suicidality (29), and 51 newer-found studies on depression.

Problems of denial by physicians and other helping professionals regarding this finding are likely, such as: 1) the possible causal relationship between trauma and subsequent mental illness and 2) the possibility of the reality of DSTS among their patients who not only don't get better but get worse on psychiatric drugs. My experience is that based on their mindset, most physicians and other helping professionals deny the first and will likely deny the second, promoting more toxic drug exposure.

10. Trauma as a cause of mental illness

Does childhood trauma cause mental illness? If we had only a few studies that looked at a small number of research subjects which showed a link between childhood trauma and a particular mental disorder, the answer would be "No". But we have the opposite [9, 10, 12].

While many clinicians suspected it for decades, before 1980 we didn't have enough data to prove a significant link between repeated childhood trauma and subsequent mental illness. Now we do. The data are clear, and for most disorders, strong. We have accumulated the data mostly since the early 1980s. Today in 2010, we have hundreds of published data based and peer-reviewed reports conducted on well over 200,000 trauma survivors and their controls (Table 5).

What makes this evidence so strong is that the authors of these reports didn't focus on a limited population using a limited method of evaluation. Instead, we have 1) *a large number of studies* (well over 300), 2) that used *a large number* of research *subjects* (well over 200,000 people). These studies were conducted by 3) multiple and independent researchers who were 4) from *different countries,* and who 5) used several *different study designs* and methods (e.g., retrospective, prospective, index cases and meta-analysis) on 6) *diverse samples* of people (e.g., clinical, community and some forensic groups). Most of these also controlled for other possible influences, which academics call confounding variables. While they sometimes used inappropriate control groups (such as other psychiatric inpatients or outpatients instead of non-mentally disordered people), which appeared to underestimate the strength of the trauma-disorder link, they still found a significant relationship between trauma and subsequent mental illness. Had they all used healthy controls, the link would have been even stronger. Furthermore, the trauma-disorder link was 7) *replicated* by nearly every one of these over 300 peer-reviewed studies. The characteristics of this large number of scientifically conducted and published studies fulfill all of the criteria for quality research reports (as summarized in Table 4.2 on page 37 of *The Truth About Depression* [49]), including 8) highly meaningful *odds ratio* results and 9) a *graded response* pattern reported in all of the studies that looked for it.

For depression (now 327 studies – I found 51 more since I published *The Truth About Depression* [49]) and alcoholism and other drug dependence (153 studies), the link with trauma is powerful. For others, such as anxiety disorders, PTSD, eating disorders, psychoses and some personality disorders, the evidence is very strong. For still others, such as behavior problems, including ADHD in children and ADD in adults, and violence, and the occurrence of revictimization and somatization (which are not mental disorders, but happen commonly with them), it is strong.

11. Conclusion

These effects of psychiatric drugs are so common and detrimental to the patient that they can no longer safely or accurately be called "side effects". Instead, they are more appropriately called toxic effects. To recognize and make the diagnosis of DSTS when it exists will take an open minded and aware

clinician who has a high index of suspicion for the possibility of its presence. It will take a clinician who can transcend their indoctrination by the drug industry and its influences that psychiatric drugs are as safe and effective as they have advertised and promoted. These drugs' effects can be and are often so detrimental to the quality of life of so many patients that they can no longer be considered trivial or unimportant [1, 6, 7, 19, 25, 26, 33–35, 37, 47–51]. Instead, they are so disruptive to many patients' quality of life that their effect becomes traumatic, and are thereby agents of trauma.

I hope that this article and its observations and preliminary data will encourage others to look into this matter in more depth.

References

[1] J.K. Aronson (ed.), *Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions* (15th edition), Elsevier Science, 2006.
[2] R.J. Baldessarini, Chapters 18&19. Drugs and the treatment of psychiatric disorders, (pp. 399–459), in: Goodman and Gilman's *The Pharmacologic Basis of Therapeutics*, J.G. Hardman and L.E. Limbird (eds), 9th ed., McGraw Hill, NY, 1996.
[3] R.J. Baldessarini and A.C. Viguera, Neuroleptic withdrawal in schizophrenic patients, *Arch Gen Psychiatry* **52**(3) (1995), 189–192.
[4] R.J. Baldessarini, A.C. Viguera and L. Tondo, Discontinuing psychotropic agents, *J Psychopharmacol* **13**(3) (1999), 292–293; discussion 299.
[5] C. Barber, *Comfortably Numb: How Psychiatry is Medicating a Nation*, Pantheon Books, NY, 2008.
[6] P.R. Breggin, *Brain-Disabling Treatments in Psychiatry: Drugs, electroshock, and the psychopharmacutical complex*, 2nd edition, Springer Publishing, NY, 2008a.
[7] P.R. Breggin, *Medication Madness: A Psychiatrist Exposes the Dangers of Mood-Altering Medications*, St Martin's Press, NY, 2008b.
[8] J.D. Bremner, *Before You Take That Pill: Why the Drug Industry May be Bad for Your Health*, Avery, 2008.
[9] J.D. Bremner, *Does Stress Damage the Brain? Understanding Trauma Based Disorders from a Neurological Perspective*, Norton, NY, 2002.
[10] J.D. Bremner, C.L. Whitfield, R. Anda, R. Lanius, C. Schmahl and E. Vermetten (In submission), A new look at trauma-related, or trauma spectrum psychiatric disorders.
[11] C. Courtois, J.D. Ford, B.A. van der Kolk and J. Herman, *Treating Complex Traumatic Stress Disorders: An Evidence-Based Guide*, Guilford, NY, 2009.
[12] B. Everett and R. Gallop, *The Link Between Childhood Trauma and Mental Illness*, Sage Publications, London, 2001.
[13] V.J. Felitti, R.F. Anda, D. Nordenberg, D.F. Williamson, A.M. Spitz, V. Edwards, M.P. Koss and J.S. Marks, Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults, *American Journal of Preventive Medicine* **14** (1998), 245–258.
[14] J. Glenmullen, *The Antidepressant Solution: A Step-by-Step Guide to Safely Overcoming Antidepressant Withdrawal, Dependence, and "Addiction"*, Free Press, NY, 2006.
[15] J.G. Gottstein, Psychiatrists' failure to inform: Is there substantial financial exposure? *Ethical Human Psychology and Psychiatry* **9** (2007), 117–125.
[16] C. Hall, C. Bergman, J. McNamara and J. Sorensen, *Harm Reduction Guide to Coming Off Psychiatric Drugs*, The Icarus Project and Freedom Center, NY and Boston, 2007.
[17] J. Harper, *How to Get Off Psychiatric Drugs Safely*, CreateSpace, TheRoadBack.org, 2005. http://www.amazon.com/How-Get-Psychiatric-Drugs-Safely/dp/1441455949/ref=sr_1_7?ie=UTF8&s=books&qid=1259165825&sr=1-7
[18] J.L. Herman, *Trauma and Recovery*, 2nd edition, Basic Books, NY, 1997.
[19] D. Healy, *Let Them Eat Prozac: The Unhealthy Relationship Between the Pharmaceutical Industry and Depression*, New York University Press, NY, 2004.
[20] D. Healy, *Mania: A Short History of Bipolar Disorder*, Johns Hopkins University Press, 2008.
[21] D. Healy, M. Savage, P. Michael, M. Harris, D. Cattell, M. Carter, T. McMonagle, N. Sohler and E. Susser, Psychiatric service utilisation: 1896 & 1996 compared, *Psychological Medicine* **31** (2001), 779–790.
[22] D. Healy and R. Tranter, Pharmacological stress diathesis syndromes, *J Psychopharmacol* **13** (1999), 287–290.
[23] L.E. Hollister, Pharmacological stress diathesis syndromes, commentary, *J Psychopharmacol* **13** (1999), 293–294.
[24] D. Inaba and W.E. Cohen, *Uppers, Downers, All Arrounders*, CNS Productions, 2007.

[25] G.E. Jackson, *Reconsidering Psychiatric Drugs*, Author House, Bloomington, IN, 2005.
[26] G.E. Jackson, *Drug-Induced Dementia: A Perfect Crime*, Author House, Bloomington, IN, 2009.
[27] H. Kutchins and S. Kirk, *Making us crazy: DSM the Psychiatric Bible and the Creation of Mental Disorders*, The Free Press, New York, 1997.
[28] R.A. Lanius, E. Vermetten and C. Pain, *The Impact of Early Life Trauma on Health and Disease: The Hidden Epidemic*, Cambridge University Press, Cambridge, UK, 2010.
[29] Legal summary cites 2010 selected: Paxil ref: http://www.businessweek.com/news/2010-07-20/glaxo-said-to-have-paid-1-billion-over-paxil-suits.html, Seroquel refs: Ref 1) http://www.businessweek.com/news/2010-02-05/astrazeneca-facing-26-000-lawsuits-over-seroquel-update2-.html, Ref. 2) http://www.bloomberg.com/news/2010-07-30/astrazeneca-says-almost-4-000-seroquel-claims-settled-through-mediation.html, Neurontin: http://www.businessweek.com/news/2010-04-01/pfizer-said-to-settle-neurontin-suicide-lawsuit-for-400-000.html, Zyprexa: http://query.nytimes.com/gst/fullpage.html?res=9f00e5db1430f936a35752c0a9619c8b63
[30] P. Lehmann, *Coming Off Psychiatric Drugs: Successful Withdrawal from Neuroleptics, Antidepressants, Lithium, Carbamazepine and Tranquillizers*, Peter Lehmann Publishing, Germany, 2005.
[31] J.H. Lowinson, P. Ruiz, R.B. Millman and J.G. Langrod, *Substance Abuse: A Comprehensive Textbook*, 4th ed., Lippincott Williams & Wilkins, Baltimore, 2004.
[32] R. Moynihan and A. Cassels, *Selling Sickness: How the World's Biggest Pharmaceutical Companies are Turning us all into Patients*, Nation Books, NY, 2006.
[33] J. Moncrieff, *A Straight Talking Introduction to Psychiatric Drugs*, PCCS Books, Ross-on-Wye, UK, 2009.
[34] J. Moncrieff, *The Myth of the Chemical Cure: A Critique of Psychiatric Drug Treatment*, Palgrave/MacMillan, UK & NY, 2008.
[35] J. Moncrieff, Why is it so difficult to stop psychiatric drug treatment? It may be nothing to do with the original problem, *Med Hypotheses* **67** (2006), 517–523.
[36] NIDA National Institute on Drug Abuse 2010, www.drugabuse.gov/infofacts/tobacco.html.
[37] J. Paris, *The Use and Misuse of Psychiatric Drugs: An Evidence-Based Critique*, Wiley, Somerset, NJ, 2010.
[38] R.K. Ries, S.C. Miller, D.A. Fiellin and R. Saitz, eds, *Principles of Addiction Medicine*, 4th edn, Lippincott Williams & Wilkins, Baltimore, 2009.
[39] B. Rothschild, *The Body Remembers: The Psychophysiology of Trauma and Trauma Treatment*, W.W. Norton & Company, New York, 2000.
[40] R.C. Scaer, *The Body Bears the Burden: Trauma, Dissociation, Disease*, Haworth Medical Press, NY, 2002.
[41] R.C. Scaer, *The Trauma Spectrum: Hidden Wounds and Human Resiliency*, Norton, New York, 2005.
[42] L. Shuster, Repression and de-repression of synthesis as a possible explanation of some aspects of drug action, *Nature* **189** (1961), 314–315.
[43] B.G. Simos, *A Time to Grieve: Loss as a Universal Human Experience*, Family Services Association of America, NY, 1979.
[44] C.J. Van Boxtel, B. Santoso and I.R. Edwards, eds, *Drug Benefits and Risks: International Textbook of Clinical Pharmacology* (2nd edition), IOS Press, Amsterdam, 2008.
[45] B.A. Van Der Kolk, A.C. McFarlane and L. Weisaeth, eds, *Traumatic Stress: The Effects of Overwhelming Experience on Mind, Body, and Society*, Guilford Press, New York, 1996.
[46] R. Whitaker, *Anatomy of an Epidemic: Magic Bullets, Psychiatric Drugs, and the Astonishing Rise of Mental Illness in America*, Crown Publishers, NY, 2010.
[47] R. Whitaker, *Mad in America: Bad Science, Bad Medicine, and the Enduring Mistreatment of the Mentally Ill*, 2nd edn, Basic Books, 2010.
[48] C.L. Whitfield, *My Recovery: A Personal Plan for Healing*, Health Communications, Inc., Deerfield Beach, FL, 2004b.
[49] C.L. Whitfield, *The Truth about Depression: Choices for Healing*, Health Communications, Inc., Deerfield Beach, FL, 2003.
[50] C.L. Whitfield, *The Truth about Mental Illness: Choices for Healing*, Health Communications, Inc., Deerfield Beach, FL, 2004a.
[51] C.L. Whitfield, *You May Not be Mentally Ill*, Muse House Press, Atlanta, 2010.
[52] R. Yehuda, ed., *Psychological Trauma*, American Psychiatric Publishing, Inc., Washington, DC, 1998.
[53] A.H. Young and A. Currie, Physicians' knowledge of antidepressant withdrawal effects: A survey, *J Clin Psychiatry* **7**(58 Suppl) (1997), 28–30.
[54] O. Zur and N. Nordmarken, DSM: Diagnosing for Money and Power: Summary of the Critique of the DSM. Online publication by Zur Institute. Retrieved 23 Aug 2010, http://www.zurinstitute.com/dsmcritique.html, 2007.

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The case of Mrs. Grundberg: A retrospective view

M.N. Graham Dukes*
Faculty of Medicine, Institute of Health and Society, University of Oslo, Trosterudveien 19, Oslo N-0778, Norway
E-mail: mngdukes@online.no

1. Introduction

Just once in a while, in the field of medical and pharmaceutical law, one encounters a case that can rightly be considered pivotal – a legal proceeding that stands out from the rest not merely by virtue of its inherent drama, but because it marked (or could well have marked) a turning point in the way in which society viewed rights and wrongs in the field. The case in which Mrs Ilo Grundberg brought proceedings against the Upjohn pharmaceutical company in 1989 for marketing a supposedly dangerous drug was one such event. It was not the first of its type, and many analogous cases in the field of pharmaceuticals were to be brought in its wake, continuing down to the present day, but after twenty years the Grundberg case merits reanalysis. Something of the events that preceded it became known at the time [9] but various writers who have sought to provide such a retrospective view [1, 4, 7, 11] have found themselves partly impeded by the secrecy surrounding certain of the events. There have been incidental revelations, notably in an industry news-sheet [2], but the story as a whole has remained untold. For Grundberg v. Upjohn never went before the United States District Court for the District of Utah. In the course of protracted depositions of a number of witnesses, the rights and wrongs of the matter had become so clear that the defendant company agreed to meet the staggering costs of an out-of-court settlement; one of the conditions of that settlement was that all the papers held by witnesses should be returned and all relevant papers should be sealed. Can one, as of 2010 and in the public interest, not dig a little deeper into the events of that time? Mrs Grundberg died in Las Vegas some years after the settlement, the Upjohn Company was absorbed into another concern and even today the files – if they still exist at all – remain sealed. But the notes and recollections of one who was closely involved in the case may provide sufficient to bring closure to the dramatic events of a generation ago and to provide some lessons for the present day.

* At the time of the initial events considered in this paper, Dr Dukes was Vice Chairman of the Netherlands Committee for the Evaluation of Medicines. Subsequently he was an expert witness in the litigation brought by Ms Ilo Grundberg.

2. The prelude

In the course of the late 1970's the Upjohn Company of Kalamazoo, Michigan, submitted to a number of national regulatory authorities a New Drug Application bearing on the compound triazolam, a modified benzodiazepine. To be known as Halcion^{R}, it was to be sold as a sleeping aid in the form of tablets variously of 0.25 mg, 0.5 mg and 1 mg. One of the agencies to which the application was submitted was the Netherlands Board for Evaluation of Medicines, which proceeded at once to review the extensive materials.

Regulatory bodies had long been familiar with the benzodiazepines, whether developed as tranquillizers, sleeping remedies or antiepileptics. They had been found to differ hardy at all from one another, except as regards their duration of action; the apparent differences in their profiles appeared to be primarily due to the fact that each had been investigated with a particular goal in view. Halcion^{R}, despite the addition of a triazolo-side-chain in the molecule, barely seemed to differ from its predecessors, except in one interesting respect: Cleared from the system within a few hours, it left behind no active metabolites. It therefore seemed to be well suited to its role as an aid to falling asleep, since all its sedative influence would have been eliminated well before morning and one would not except to encounter the sort of residual somnolence that could cause problems in the daytime. With this view apparently amply confirmed by the evidence from clinical studies, the file was soon approved and in the course of 1978 the drug was marketed in The Netherlands and elsewhere.

The initial sales of any new pharmaceutical are likely to be limited, and one cannot during the first few months anticipate any substantial feedback from the field. Oddly, however, in the case of Halcion^{R}, unusual reports of suspected unwanted effects of the drug began to trickle into Holland's Adverse Reactions Monitoring Centre almost from the start. A number of users of the drug, it would seem, had been behaving oddly and sometimes unpleasantly. The evidence was however still fragile, and little more could be done than to keep a careful watch on any further development that might emerge. And so things might have continued had it not been for Dr van der Kroef. A psychiatrist working in The Hague, Dr van der Kroef had first prescribed Halcion^{R} late in 1978 to a lady of 53 in whom other products had failed to relieve her insomnia. The insomnia was indeed relieved but as the psychiatrist wrote later:

> "Mentally she rapidly went downhill. Progressively she became paranoid. Several times she asked me what the new hypnotic contained – LSD perhaps? – for she felt that she was bordering on a psychosis. She felt shut off from the world: It was as if she no longer belonged in society. Her friends asked her what was happening to her, so strangely was she behaving..."

Other symptoms followed and after some weeks Dr van der Kroef withdrew the Halcion^{R} and prescribed nitrazepam in its place. The relief was immediate and dramatic but for Dr van der Kroef not entirely unexpected, for in the meantime he had observed similarly alarming changes in three other patients during their use of Halcion^{R}. By now thoroughly concerned, he reported his experiences in a manuscript for publication in The Netherlands weekly medical journal [13], dutifully copying his text to the Adverse Reactions Monitoring Centre and submitting a shorter version of his findings in a letter to the *Lancet* [14]. At the beginning of July 1979 his paper was published in The Netherlands; and its effect was much reinforced by the prompt appearance of large headlines in a popular daily newspaper, hungry for seductive headlines in the middle of the holiday season. What followed was described in a contemporary account as national uproar. The health authorities found their mailbags filled and their telephone lines jammed by a massive reaction, both popular and professional, much of it seemingly confirming Dr van der Kroef's findings, but here and there contesting them. Seeking

to get at the hard truth of the matter, the Adverse Reaction Monitoring Centre circularized the country's physicians, enlisting their help. Within two weeks six hundred further reports of suspect adverse effects to Halcion^{R} – mostly mental changes, in some cases amounting to psychosis – had flowed in, and hundreds more were to follow; particularly striking were the repeated accounts of bizarre acts while sleepwalking, aggressive and hostile behaviour and suicidal or homicidal intent. In some cases the nightly dose of Halcion^{R} had been as high as 1 mg, but in many no more than 0.25 mg or 0.5 mg had been ingested.

By now, restrictive measures clearly seemed to be called for. The Board for the Evaluation of Medicines suspended Upjohn's marketing licence for the drug for the maximum permissible period of six months. At the end of that time, following a further careful evaluation of the evidence that included personal interviews with many of the reporting physicians and a number of patients, the manufacturer was confronted with the Board's conclusions; the Board was willing to permit reintroduction of the product at a much lower dose and with strict restrictions on labelling, but the manufacturer refused to agree and withdrew Halcion^{R} from the Dutch market. Other European countries, initially sceptical on the matter, in due course experienced similar problems and in essence, though each in its own way, duly followed Holland's example. The United States took a different course. The Food and Drug Administration set up a Panel to study the matter, which reported in September 1979. After working in close consultation with the Upjohn company the Panel concluded that for the vast majority of users Halcion^{R} was a safe drug; the firm was lauded for its attention to adverse reaction reporting; surprisingly, the panel chose to castigate the FDA's own monitoring system for its unreliability, flooded as it was declared to be by unreliable reports of mere suspicions. There had indeed, as the Panel noted, been some smoke billowing across the Atlantic, but it was merely smoke without fire. Halcion^{R} could and should remain on the U.S. market.

3. Enter Ilo Grundberg

While the FDA Panel was still deliberating its conclusions, the present writer was telephoned in Europe by a law firm in Atlanta, Georgia, to request technical support in dealing with a matter relating to the supposed risks posed by Halcion^{R}. The story was as different as it could be from the picture painted by the Panel. As related briefly over the phone it related to a divorcee, 57 year-old Mrs Ilo Grundberg, who had for some months lived in a trailer in Utah with her mother to whom she was deeply devoted. Suffering from insomnia, Mrs Grundberg had been treated with Halcion^{R} for several periods over the course of a year. During each period of treatment she had experienced symptoms reminiscent of those reported in Holland, in particular notably marked paranoia and personality changes. Ultimately, while taking the drug, she had late on the evening of June 19th 1988 taken out a gun and shot her mother eight or nine times through the head. Some hours later she had telephoned her daughter, Janice Gray, to tell her what she had done. Janice promptly rang the deputy sheriff who arrived to find Ilo standing beside her mother's bed; immediately ready to confirm the killing which she attributed to her love for her mother. In the course of the night she was duly arrested on suspicion of murder.

With the case due to be heard before the criminal court in Utah as one of second-degree murder, she had already been admitted to a psychiatric hospital in Salt Lake City for examination. In the light of their findings, two psychiatrists appointed by the court testified that Ms Grundberg had been "involuntarily intoxicated" when she killed her mother; in response, the prosecutors asked the court to dismiss the case; in February 1989 she was released. Then it was that she approached the firm of trial lawyers in Atlanta with a proposal to bring civil proceedings against the Upjohn company for its having marketed

a dangerous drug that had injured her personally and caused the loss of her mother; $21 million was claimed in damages.[1]

4. Documents in the case

Later in 1989, with an agreement signed to appear as an expert witness in the civil proceedings, massive documentation relating to the case became available. In line with U.S. legal procedure, the trial lawyers acting for Mrs Grundberg had the right to access the internal documents of the defendant company and they did so with great thoroughness. As they proceeded, a number of acute surprises were encountered. In particular, the Upjohn files proved to contain relevant material on the clinical investigation of Halcion^{R} that had clearly not been laid before the regulatory authorities in The Netherlands, the United States or elsewhere.

There was, for example a placebo-controlled study in prisoners, known as Protocol 321, that had been conducted between 1972 and 1973. It had indeed been submitted to the Food and Drug Administration and to other authorities, but edited in such a manner that the drug appeared to have been well tolerated. In actual fact, various individuals receiving the drug in a 1 mg dose this study had experienced paranoia, delusions or "weird thoughts" to an extent that strongly suggested psychotic changes. In a number of other studies that were brought forward for review, known as Protocols 6023, 6047 and 6049, the dropout rate because of side effects had been strikingly high for patients receiving Halcion^{R}, even in a dose of 0.5 mg; among the effects noted were amnesia, incoordination, restlessness, nervousness, bizarre night terrors and states of confusion.

The gloss put upon these and other studies by the defendant company in its contact with regulatory authorities was maintained despite the fact that, well before Mrs Grundberg killed her mother, the firm was also becoming increasingly aware of a series of cases from the field in which Halcion^{R} appeared to have been involved in suicidal or homicidal behaviour. Early in 1987 a medical director in the firm found it possible had been able to draw up a 24-item "List of Murders, Attempted Murders, Threats of Physical Violence Reported with triazolam". A footnote to the report noted that there were also further instances known to the firm of aggressive, hostile or combative behaviour, including four involving criminal acts. The material in the body of the report itself was however sufficient to elicit grave concern. In July 1982 a patient in a Halcion^{R} trial in the United Kingdom had committed suicide. In 1983 a former Kalamazoo policeman had attempted to kill his wife, only to be acquitted because of his use of Halcion^{R}. Other relevant cases flowing into the company's files pointed in the same direction. In one Canadian case, a Halcion^{R} user had prepared a glass of cyanide in order to commit suicide; he then fell asleep, and woke up to find that he had murdered his wife and daughter. In France, the wife of a Halcion^{R} user had woken to find her husband pouring oil onto the floor with the intent of burning down the house; in another instance from France a man had bought cartridges in order to kill his family and the neighbours. There were many other reports to hand.

[1] The suit brought against Upjohn was for "negligence and wrongful death". The complaint was *inter alia* that Halcion^{R} was "unreasonably dangerous, unsafe for its intended use and defective because of its tendency to cause intoxication in the user when used properly and according to the advice and directions supplied by the defendant". There was a concurrent alternative claim that Upjohn sold Halcion^{R} in a dangerous, excessive dose, far beyond any reasonable and responsible margin of safety. General and specific claims referred to a series of adverse effects including the risk of homicide.

5. Evidence on the facts

In accordance with U.S. legal practice, both factual and expert witnesses from both sides were by now being deposed, i.e. they were being presenting their testimony in a closed session with both legal teams and were being questioned extensively by lawyers from opposing parties as to both their evidence and their qualification to provide it. The proceedings at these depositions were noted verbatim by a court reporter for presentation to the Court.

Evidence on the facts of the case provided a remarkably detailed picture of the bizarre events on the fatal night of June 19th/20th, 1988. Deputy Sheriff Reg Brown, alerted by Janet's telephone call, had entered the trailer at about 3.15 a.m. in the morning to find Ilo Grundberg standing beside her mother's bed, apparently somewhat confused but a written confession in front of her. In her mother's cold hand was a birthday card from Ilo bearing the words "It was going to be your worst one, Mom". After shooting her mother, Mrs Grundberg had taken the time to go to the shower, to write various letters as well as the confession, and to set about washing some clothes, before telephoning her daughter at 2.30. A medical examiner who reached the trailer at 3.45 a.m. noted Mrs Grundberg as stating that she had killed her mother out of love. By 6.30 in the morning in a police interview she was remarking: "I don't know why I did it. . ." but adding by way of explanation: "I thought rather than go through what's coming up she'd be better off with Daddy". A letter that Ilo had written to her daughter around midnight echoed the same theme: She feared that something terrible was going to happen, and that with her birthday approaching her mother should not live to experience it. Later on the day of June 20th when Janice visited her mother in prison she found her anxious and confused but apparently aware of the killing ("I can't believe I did this – I can't believe this happened").

Dr Groesbeck, one of the psychiatrists who had examined her at the request of the criminal court, now confirmed at deposition that Mrs Grundberg had been suffering from "involuntary intoxication", sufficient to cause severe damage to "judgement, perception and awareness", while on the night of the killing she had been suffering some memory loss, along with confusion.

Janet Gray for her part described how, during the months prior to the killing, Mrs Grundberg had been suffering from unusual symptoms; she exhibited nervousness; at times she had been hostile and sarcastic; she had also developed persistent paranoid ideas, including the notion that the neighbours had set up "a radar dish" to spy upon her since she was not "taking care of Grandma". Unemployed, she was convinced that the State "was going to take her to jail because the employment bureau had set up two interviews which she had failed to keep", that she was going to be ejected from her home. That everyone was trying to "get her" and that she and her mother were virtual "prisoners in the house".

With the basic facts of the case thus established, the series of depositions and expert reports now turned to the question as to whether Halcion^{R} could in view of its nature have been the essential element that led Mrs Grundberg to kill her mother. Crucial to Mrs Grundberg's case was the evidence of Prof. Ian Oswald, a Scottish psychiatrist who had developed polysomnography as a means of examining the effect of pharmaceuticals on electrical activity in the brain, particularly during sleep, but who had also examined the efficacy and safety of Halcion^{R} in the clinic. His findings amply confirmed those of Dr van der Kroef and others, and in the months that followed Prof. Oswald was to repeat emphatically in the media and elsewhere his view that Halcion^{R} was, in the doses in which it was intended to be used, a risky drug. In his opinion Upjohn had misled the regulatory authorities into approving a medicine that in fact had no place in the market. He was supported vigorously by Dr. Anthony Kales, head of psychiatry at Pennsylvania State University Medical School. No other benzodiazepine had in his view such a narrow margin of safety as did Halcion^{R}.

Vigorously opposing these expert views were the declarations of witnesses advanced by the defendant, including both external specialists and members of Upjohn's own staff. Dr Michael Kleerenkoper of the Henry Ford Hospital in Detroit pointed to evidence that Mrs Grundberg was suffering from hyperparathyroidism, suggesting that this would be sufficient to explain her deviant behaviour. In this view he was supported by Dr William Logan from Kansas and Dr Lincoln Clark of Utah. Their suggestion that hyperparathyroidism was responsible was however in all probability a red herring since her blood calcium was only marginally raised and had been stable for several years. However, Dr Logan himself, having examined Mrs Grundberg prior to his deposition, also testified that in his view she was suffering from ". . .the failure of characterological methods of coping with anger and hopelessness through repression, minimalization and denial, to sustain her through the stress that she was experiencing, as well as her view of death as a relief from suffering". In a note to the defence lawyers, Dr Logan had expressed more concisely the view that "Mrs Grundberg appeared to be suffering from a major depressive disorder, recurrent with mood congruent and incongruent features. . .".

Other experts called for the defence similarly sought to explain her behaviour as being precipitated by factors other than her use of triazolam. There was indeed some reason to consider that, in addition to possible endogenous depression, for which she had at times received various antidepressant agents, she had also been suffering from anxiety. Might there not also be a family element? Mrs Grundberg's late father had been depressed and had suffered mental breakdowns, while an aunt was known to have attempted suicide. Mrs Grundberg herself, her father and her daughter Janice all had a history of alcoholism; Ilo herself had experienced a stressful childhood and an extremely unhappy marriage, and was believed on one occasion to have contemplated suicide. Janice was now at the age of 27 already married for the fourth time. And if drugs were involved at all in the matter there was a variety from which to choose; Mrs Grundberg's prescription record pointed to her having received supplies of acetaminophen combined with codeine, as well as quantities of an estrogen, ibuprofen, trazodone, diazepam, verpamil, amitryptyline, trimipramine and alprazolam; there were apparently ample quantities of drugs within reach in the bathroom, probably including a residual supply of Halcion^{R} that had for a time been prescribed for her mother. Even if Halcion^{R} were to be held in some measure responsible for the course of events, was there any certainty that Ilo had taken it in a proper dose? Was there not some reason to believe that she had also taken Valium (diazepam) and codeine on the day of the killing? Her own statements on her recent use of medicines seemed to be inconsistent. Finally, was there not some – admittedly disputed – evidence that after the killing Mrs Grundberg had been prescribed Halcion^{R} once more while in prison and had at that time tolerated it perfectly well.

At one point it was argued, if somewhat cautiously, that Mrs Grundberg's killing of her mother was in some measure understandable. The old lady was apparently suffering from mental changes, probably attributable to atherosclerosis and it had become increasingly difficult to live with her; Mrs Grundberg had already applied for her mother to be admitted to a home for the demented elderly. No-one was suggesting that her mother was better off dead, but one needed to have some understanding of the stressful situation in which Mrs Grundberg found herself, and matricide was by no means an unknown phenomenon in America – according to one estimate advanced during deposition there were some 1600 cases yearly.

One contested element in the defence was the outcome of a re-examination of Mrs Grundberg's mental state that was carried out at the specific request of Upjohn's team in the Menninger Clinic in Houston, Texas, in March 1990, i.e. 21 months after the killing. The findings in a long series of tests formed the basis of Dr Logan's testimony, but the psychologist Lipson presented his own conclusions regarding her psychological profile. In his view this was consistent with that of persons known to have engaged in violent acts; Grundberg had a "super-ego" but "stuffed her feelings" so as not to exhibit the aggressive and

belligerent feelings that she might be experiencing. He compared her condition to that of "a time-bomb waiting to go off" in the form of violent outbursts. Mrs Grundberg questioned the relevance and validity of these late findings; was it not so that she had agreed, perhaps reluctantly, to undergo these tests to satisfy the defendant and might this not have affected her performance at the clinic? The answer appeared uncertain.

For much of the time the defence team, setting aside the particular circumstances of Mrs Grundberg's case, followed Upjohn's general line on Halcion^{R}, seeking to demolish the casuistic evidence that it was an unusually risky drug. Various witnesses for the defence pointed in particular to supposed weaknesses in the body of evidence linking Halcion^{R} to aggressive or homicidal behaviour. Many of the relevant reports were dismissed as "anecdotal" or incomplete; patients allegedly suffering from such complications were commonly mentally unstable to begin with. Above all, it was argued, the reports of suspected adverse reactions received by national centres and cumulated by the World Health Organization proved nothing; they were flimsy in quality and negligible in quantity, certainly in the United States where sales of the drug had risen rapidly yet no more than 1700 suspected adverse events to it had been reported over some six years of marketing. That particular argument was in fact weaker than it seemed; at the time the Food and Drug Administration was freely admitting to all who would listen that the proportion of suspected adverse drug effects that was reported to its system was only a small fraction of those that should in fact have reached its files; a figure of less than 1% was cited, rising to some 10% in the case of serious reactions. If, as seems likely, a similar degree of under-reporting of suspected adverse effects prevailed at the time in other national systems[2], the occurrence in the cumulated WHO records by 1990 of 204 reports of delusions, 89 of attempted suicide, 44 of psychosis and 72 of aggressive reactions could indicate that serious complications of Halcion^{R} use were by no means uncommon.

Despite such counter-arguments, the evidence that Mrs Grundberg had truly and gravely suffered from the effects of Halcion^{R} continued to mount as the depositions proceeded. The spectrum of apparent adverse effects during the months preceding the killing closely paralleled the picture emerging from numerous adverse reaction reports. Whether on the fatal night of June 18th the drug had acted alone or had simply triggered an acute reaction to which she was already predisposed remained in dispute, but it had almost certainly played a cardinal role. At times it seemed as if the defence, perhaps sensing that it was losing ground, was tempted to disconcert expert witnesses by resorting to curious methods almost from the realm of legal legend.[3] During one deposition, a witness engaging in a solemn analysis of the events leading up to the killing found himself faced at a given moment with quiet giggling from the defence, seemingly to suggest the utter absurdity of his arguments; at another tense moment a defence lawyer began scratching himself vigorously in the manner of an ape. During yet another session a heavy book was thrown at a witness who had questioned its relevance, while one expert was able to discern from the manner of questioning that an extensive enquiry had been conducted into his personal affairs. Dr Ian Oswald, to cite just one name, found himself faced condescendingly with a demand to know whether he had ever obtained proper certification in polysomnography in any American State; he was able to reply that, as the pioneer of polysomnography, he had no need of such a diploma.

Whether such incidents were no more than expression of fatigue or mere mischief or perhaps pointed to a measure of despair one will never know. Nor will one ever be sure as to which elements in the case, as delineated during the depositions, essentially led the Upjohn company shortly thereafter to settle the entire matter with Mrs Grundberg, out of court and at very considerable expense. Other settlements in

[2] In the United Kingdom the overall reporting rate for adverse reactions was estimated at 5%.

[3] "If you can't win on the facts, argue the law. If you can't win on the law, call the other lawyer names." – *old saying.*

analogous cases involving the drug were to follow. As a commercial product, Halcion^{R} was destined to remained in limbo in much of the world for a considerable period, only re-emerging later for use in recommended doses that were a mere fraction of those in which it had originally been launched into the world of medicine.

The Grundberg litigation had one direct aftermath. Dr Ian Oswald, who had expressed both in the *New York Times* and on BBC Television his view that the company had essentially lied to the regulatory authorities, found himself arraigned for libel by the Upjohn Company before the High Court in London, as did the British Broadcasting Corporation. After lengthy proceedings, the company was awarded substantial damages in both cases. For the casual reader and viewer, unaware of what had gone before, it may well have seemed that Halcion^{R} had been exonerated after all.

6. The case in retrospect

Examining once more the evidence of two decades ago, the parallels between the case of the unhappy Mrs Grundberg and the patients on whom Dr van der Kroef and others had reported earlier are so striking that her case would very probably have prevailed in court. The severe and systematized paranoia was particularly striking, but nervousness, confusion, anxiety and restlessness over the months were all in evidence; she had experienced both hypaesthesia and hyperacuity; and both her daughter and her neighbours had been very aware of a change in her character during her months of treatment with Halcion^{R}. There was expert evidence of her suffering from (possibly anterograde) amnesia at the time of the killing, and there seemed to be no doubt that on that fatal night of June 18th, that she was in a psychotic state. In addition there was a history – admittedly an uncertain one – of responses to dechallenge and rechallenge on one or more occasions. Initially she had taken a daily dose of 0.25 mg of Halcion^{R}, but this had later been raised to 0.5 mg and she seems to have asked her family doctor whether she could double this dose when she needed to do so.

Nevertheless, taking together the arguments and evidence advanced by the two opposing parties, a complex picture emerges. As concluded above there was considerable reason to believe that Halcion^{R} had both progressively altered her mental state and then triggered the events of June 19th 1988, but these things had occurred in an individual who was perhaps unduly sensitive to this type of drug complication by virtue of her age, her difficult and stressful circumstances, her apparent history of mental inconstancy and the pharmacological arsenal to which she had been exposed. With the wisdom of hindsight one may well observe that Mrs Grundberg should never have been prescribed Halcion^{R} at all or only for very brief period and in a reduced dose; but the labelling of the time provided no adequate guidance to the physician on the matter, neither specific study of the drug's effects in such high-risk individuals nor determination of the lower effective dose had ever been carried out, and Upjohn had triumphantly defeated an FDA proposal to limit its use to fourteen days. Given this history it is hard to put any part of the blame on the prescriber, much less on the victim; but it could well explain why the defendant company did not wish to see the entire picture exposed to public view in court proceedings.

In the recent past, Prof. Deborah Denno of Fordham University School of Law has argued cogently called for reconsideration of the rigid distinction made in American law, when assigning criminal liability, between voluntary and involuntary acts. To quote her literally:

> "... modern neuroscientific research indicates that the boundaries between our conscious and unconscious states are permeable, dynamic, and interactive. To enable the law to join science in a more

nuanced and just view of the human mind, this article proposes that, in addition to voluntary and involuntary acts, the criminal law recognize a third category – semi-voluntary acts" [6].

It would seem entirely possible that the mental state of Mrs Grundberg, when she took the gun to her mother, was such that the killing could best be regarded as a semi-voluntary act. Such a classification could have proved helpful both when a criminal charge was laid against her and in assessing her subsequent civil complaint.

7. The company's acts and omissions

Looking back over two decades, and particularly bearing in mind the evidence that came forward in the Grundberg case, it is fair to suggest that over a considerable period the Upjohn company repeatedy failed to act in its own best interests, or those of the patient, where Halcion^{R} was concerned.

Firstly, the totality of the records available by the time of the Grundberg depositions seemed to show that Halcion^{R} could be an effective hypnotic in a dose of no more than 0.25 mg, a conclusion that had already been advanced within the company by members of the firm's own medical staff. Upjohn nevertheless proceeded to market it in tablet strengths of up to 1 mg, a dose that was in many cases likely to be excessive and to be capable of inducing unwanted and sometimes serious reactions. As already noted, no sufficient attempt seems to have been made to determine the lowest effective dose, or to study the extent to which the drug would be tolerated by elderly or other weakened subjects.

Secondly, in exhibiting contempt for the growing worldwide evidence of risk attaching to Halcion^{R}, the firm clearly failed to appreciate the very reasonable view put forward by investigators such as Oswald that a short-acting benzodiazepine derivative without active metabolites might well induce, either at night or during the next day, a severe withdrawal reaction. Withdrawal reactions to benzodiazepines as such were already well recognized, but with the persistence and gradual decline of active metabolites following ingestion of the older drugs such reactions had been gentler, delayed, and altogether much less common. With triazolam the sedative effect would fall acutely after some hours precipitating a much more marked withdrawal effect, sufficient to derange a sensitive system.

Thirdly, the company's approach to national regulatory authorities left much to be desired. It was as if truth had become in some degree a flexible commodity that could be moulded to suit a firm's convenience. The manner in which early evidence of severe unwanted effects, especially those encountered in the prison study 321, was hidden from view was neither wise nor particularly edifying. Only under much pressure did the company ultimately concede (for example to the regulatory agency in Britain) that it had – supposedly because of a "transcription error" – deleted incriminating data from that study when submitting it to the authorities [12]. One might in all fairness add however that regulatory agencies, for their part, may need to be more cautious than they have sometimes been when considering the merits of a new drug that seems to be closely akin in structure to an existing class; very minor alterations in a molecule may have more drastic consequences than is sometimes appreciated. In quite another field, that of inflammatory agents, some ugly surprises encountered with benoxaprofen (Opren^{R}) and two decades later with rofecoxib (Vioxx^{R}) underscore the same lesson.

Fourthly, one is obliged regretfully to conclude that, even after the problems with Halcion^{R} had all too clearly raised their heads, the company saw fit to deny their existence to an FDA Panel that had been constituted to examine that specific issue, providing the latter with apparent grounds to give Halcion^{R} a clean bill of health. The Panel was assured at various points during its proceedings, and quite incorrectly, that most of the adverse reaction reports in The Netherlands came from a single physician, that the reported

cases had never been adequately documented, and that all the reports related to the 1 mg dose. There was no admission to the Panel that the firm had known of the possible risks since the time of the prison study 16 years beforehand. One staff physician went so far as to assure the Panel that all the "unwanted" effects attributed to Halcion^{R} were mere expressions of its sedative activity. One might add that when Upjohn, seeking to recruit allies to combat what it was now terming "the Dutch disease", convened a "thought leader conference" in Boston in 1979 under the chairmanship of Dr Frank Ayd it failed to inform the participants of the findings in Protocol 321, a study of which Dr Ayd only became aware much later [3].

Above all, the Upjohn company seems over a period of years to have chosen to ignore repeated warnings from one of its own staff physicians, Dr William Barry. Evidence in the Grundberg case showed that, from his position with the firm's drug experience unit, Dr Barry had repeatedly but to little avail urged the company's commercial management to pay due attention to the emergent problems with triazolam.

8. A final lesson

Not until 1999, a decade after the Grundberg depositions, did the Institute of Medicine in the United States publish its own "Independent Assessment of Safety and Efficacy Data on Halcion^{R}" [5] that it had undertaken at the request of the Food and Drug Administration. The study made use of data released variously by the Administration itself, the manufacturer, and a number of the scientific institutions involved in the study of the product. By that time, however, many a lesson had been well and truly learnt by all parties from hard experience. Halcion^{R} still featured on American pharmacy shelves and had attained massive sales, but it was now offered for short term use only, and in doses commonly amounting to a mere eighth of those at which it had been launched, while its labelling was replete with exemplary precautions and warnings:

> "Halcion is indicated for the short-term treatment of insomnia (generally 7–10 days). Use for more than 2–3 weeks requires complete re-evaluation of the patient. Prescriptions for Halcion should be written for short-term use (7–10 days) and it should not be prescribed in quantities exceeding a 1-month supply".
>
> "The recommended dose for most adults is 0.25 mg before retiring. A dose of 0.125 mg may be found to be sufficient for some patients (e.g. low body weight). A dose of 0.5 mg should be used only for exceptional patients who do not respond adequately to a trial of a lower dose since the risk of several adverse reactions increases with the size of the dose administered. A dose of 0.5 mg should not be exceeded. In geriatric and/or debilitated patients the recommended dosage range is 0.125 mg to 0.25 mg".

The summary list of adverse reactions referred to weak or shallow breathing; fast or pounding heartbeats, confusion, slurred speech, unusual thoughts or behaviour and hallucinations; the complete list of possible side effects now made specific reference to agitation, aggression and thoughts of suicide.

Somewhat surprisingly the Institute's report was at pains to reject the "belief" that Halcion^{R} could elicit any unique pattern of injury, unknown with more traditional benzodiazepines. In a sense the writers were here tilting at windmills, since no-one (with the possible exception of the good Dr van der Kroef himself in the early days) had ever seriously suggested that the distressing reactions seen with Halcion^{R} were entirely unique. A literature review [8] drawn up for regulators at the time specifically made the point that all these reactions had been seen at some time with earlier compounds but that they had been excessively

rare. In essence, as noted above, they represented withdrawal reactions; their particular frequency and severity in the case of Halcion[R] reflected primarily the fact that the compound had no active metabolites and that it was at the time being used in excessive doses, especially in subjects who might have been expected to be particularly susceptible to such adverse effects.

Beyond that the Institute advanced a series of useful proposals regarding the desirability for better studies of sleep and more reliable evaluation of hypnotic medications as a group. It also found it necessary to plead for the further study of certain aspects of Halcion[R], including its tolerance in the elderly; had that latter need been appreciated by company management twenty years earlier much misery might have been avoided.

It is good that such an assessment as that undertaken by the Institute could in due course be carried out, independently of any of the parties earlier involved. All the same, one regrets that much of the Grundberg story was confined so promptly and so firmly to obscurity. In recent years, there has been an increasing realization of the need for transparency in matters of drug regulation [1]; much the same holds good where out-of-court settlements are concerned. A great deal of misunderstanding and harm could surely have been avoided had the evidence in the Grundberg case been opened to wider scrutiny and discussion. One is bound to wonder, too, whether the libel action brought in London against Professor Oswald and the BBC could possibly have succeeded had all the evidence on the doctoring of Protocol 321 been accessible; the true facts of that matter did ultimately become available through other channels [10] but too late to affect the decision of the High Court. The overall history of Halcion[R] has been sketched in many and excellent writings, but one element has been largely lacking; a dispassionate reanalysis of the manner in which the tragedy of Ilo Grundberg was handled – or mishandled? – around a table in Atlanta. Looking back to those events can surely provide a valuable lesson for those dealing with similar situations at the present day or in the future.

References

[1] J. Abraham, Transnational industrial power, the medical profession and the regulatory state: Adverse drug reactions and the crisis over the safety of Halcion[R] in The Netherlands and the UK, *Soc Sci Med* **55**(9) (2002), 1671–1690.

[2] Anon., Upjohn's Halcion[R] data to be disclosed, *Scrip* **1630** (1991), 14.

[3] F. Ayd, Affidavit, Maryland, USA, 7 December, 1992 (as cited by Abraham, see above).

[4] C. Bogus, *Why Lawsuits are Good for America*, NYU Press, New York, NY, 2003.

[5] W.E. Bunney, D.L. Azarnoff, V.W. Brown, et al., Report of the institute of medicine committee on the efficacy and safety of Halcion[R], *Arch Gen Psychiat* **56** (1999), 349–352.

[6] D.W. Denno, Consciousness and culpability in American criminal law, *Waseda Proc Comp Law* **12** (2009), 115–126. Fordham Law Legal Studies Research Paper No. 1483880.

[7] D.W. Denno, Crime and consciousness: science and involuntary acts, *Minn L Rev* **87** (2002), 269–401.

[8] M.N.G. Dukes, Excitation and other psychic reactions to benzodiazepines, 1987 (Unpublished).

[9] M.N.G. Dukes, The van der Kroef syndrome, *Side Effects of Drugs Annual* **4** (1980), v–ix.

[10] C. Dyer, New report criticizes Upjohn over Halcion[R], *Brit Med J* **308** (1994), 321.

[11] R.H.B. Meyboom, The triazolam experience in 1979 in The Netherlands: A problem of signal generation and verificationm, in: *Drug Epidemiology and Post-Marketing Surveillance*, B.L. Strom and G. Velo, eds, Plenum Press, New York, 1992.

[12] Royal Courts of Justice, *Judgement between the Upjohn Company and Upjohn Ltd and Professor Ian Oswald and between Dr Royston Frederick Drucker and Professor Oswald and between the Upjohn Company and Upjohn Ltd and the BBC and Tom Mangold before Mr Jutice May*, Beverley F. Nunnery, 27 May 1994.

[13] C. van der Kroef, Halcion[R]: Een onschuldig slaapmiddel? *Ned T Geneesk* **123** (1979), 1160.

[14] C. van der Kroef, Reactions to triazolam, *Lancet* **2** (1979), 526.

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The 2010 U.S. health reform legislation: Evaluating the experiment

Marshall B. Kapp
Director, Center for Innovative Collaboration in Medicine & Law, Florida State University, 1115 W. Call Street, Tallahassee, FL 32306-4300, USA
Tel.: +1 850 645 9260; Fax: +1 850 645 2824; E-mail: Marshall.kapp@med.fsu.edu

In the early part of 2010, the United States Congress enacted, and President Barack Obama signed into law, the Patient Protection and Affordable Care Act (PPACA) [18]. This massive (more than a thousand pages) piece of federal legislation purports to reform the entire American health care financing and delivery enterprise in ways that will demonstrably improve the quality of health care and its accessibility and affordability for the populace.

In widespread public debates and private arguments about the PPACA, both while a multitude of different versions were under legislative consideration and since enactment of the final Act, contrasting claims have been made by proponents and opponents regarding specific projected results of the Act's passage and implementation. Even though (shamefully) members of Congress openly (in some cases almost proudly) admitted that they had not read, and did not know the contents of, the bill upon which they were voting, legislators on both sides of the aisle were influenced – to whatever extent they were not driven by pure politics – by their respective assumptions about the specific salutary or deleterious effects that they expected to emanate over time from the changes made by the PPACA. In many respects, the *a priori* assumptions of both PPACA advocates and critics rested more heavily on ideological faith and gut instinct than on carefully informed reasoning.

As elegantly enunciated by an official of the American College of Physicians:

> Listening to much of the commentary after President Obama's signing of the PPACA of 2010 into law on March 23, you might think that the United States suddenly developed a machine that allows us to see into the future. Supporters of PPACA confidently assert that it will lead to better and more affordable health care for everyone, reduce the deficit, and lower premiums. With equal certitude, critics state that it will lead to rationing, more debt, and higher premiums. *** I think that we should all take a deep breath, put politics aside for the moment, and evaluate the law's impact objectively. Supporters and opponents alike must humbly recognize that no one knows how this complex legislation will play out [5].

Put much less elegantly,

> [W]e still haven't figured out what we're going to do about it [the national debt]. Except, perhaps, make it worse, as nobody, not even the big brains over at the Government Accountability Office or the Office of Management and Budget, has any idea of how health-care reform will affect long-term deficits and the solvency of the United States of America [3].

It clearly is true that, at this time, we do not know whose assumptions, and which particular assumptions, will turn out to be accurate projections about the future of American health care. It is much too soon today to determine whether the PPACA will ultimately be the legal vehicle for wonderful health care utopia or the terrible instrument of health care demise in the U.S. However, within a reasonably foreseeable time frame, the American electorate can expect to have a strong informational foundation on which to judge the wisdom of those who took on prominent roles in the PPACA debates – including politicians, trade associations, advocacy organizations, and private foundations with particular ideological proclivities – and to hold those policymaking participants accountable for the good and bad impacts of the new law. Answers will indeed be available.

Given the many radical modifications the PPACA will make in the ways that the various American parties provide, receive, and pay for health care, the health reform law might be characterized, as it is implemented in several stages over the next decade, as an enormous social engineering experiment being conducted without the approval of any Institutional Review Board or the informed, voluntary, mentally capable consent of any of its individual human subjects. We need to take advantage of the opportunities for understanding more about the intricacies of health care financing and delivery that this social engineering experiment – "a hodge-podge . . . involve[ing trial and error]" [8] – will afford us. Over the next several years, data about all facets of the health care system will be commandeered from health care providers, insurers, employers, and regulators and amassed based on this experiment. We will have the means to determine whose predictions were correct and whose were not.

This extensive database can and should be analyzed and translated into useful information about the successes and failures of the PPACA as a health reform experiment. It has been recognized that "Implementation of a national insurance system might influence access and receipt of care for patients in unpredictable ways in different jurisdictions that have different baseline mechanisms of funding; this is an area in need of further research" [7]. Interestingly, although the PPACA authorizes many new initiatives involving research into best medical practices, as a basis for the federal and state governments eventually promulgating regulations further restricting physicians' professional judgment in caring for their patients (for instance, in Section 6301 creating a Patient-Centered Outcomes Research Institute), the Act does not authorize any research program specifically tasked with examining the actual impact of the Act itself on its various constituencies.

A variety of potential funders ought to, as a matter of pursuing the public interest, support a research portfolio in this arena. In the federal government sphere, this kind of knowledge generation falls squarely within the missions of the Agency for Health Care Research and Policy, Centers for Medicare and Medicaid Services, Health Resources and Services Administration, and the National Science Foundation, among other agencies. Individual states, and especially their Medicaid agencies, should be very interested in supporting this endeavor, as should a panoply of private foundations that focus on health policy formulation and evaluation.

There are virtually an infinite number of discrete but related questions that might profitably be included as part of a health reform research agenda. A very cursory but illustrative sample of questions that only begin to comprise a comprehensive effort to evaluate the actual quality, access, and affordability impacts of PPACA might include the following:

- Has the Quality of American Health Care Improved Under the PPACA?
    - Does the PPACA provide a stimulus for the conduct of comparative effectiveness research that improves the quality of patient care, or that opens the door to government-driven (through payment rules, control of available resources, or direct regulation of health care providers) rationing

of beneficial health services? [6, 15] Does it stimulate the conduct and use of comparative effectiveness research that pays sufficient attention to population health? [12]
    - Post-PPACA, what are the differences in patient outcomes, in terms of both mortality and morbidity? What is the Act's impact in terms of primary and secondary prevention of disease, and in terms of treatment of acute and chronic medical conditions? [13]
    - What impact (if any) does the PPACA have on individual health-related behaviors, such as smoking and excessive eating? Does the Act encourage health prevention behaviors or discourage them?
    - What are the implications of the PPACA for the protection of private medical information about individual patients? [16]
- Do Changes in Quality, Accessibility, and Affordability Attributable to the PPACA Affect Different Population Groups Disparately?
    - Who are the relative "winners" and "losers" created by the Act? [17]
- Has Health Care Become More Accessible to the Public Under the PPACA?
    - Do requirements in the Act encourage or discourage private health insurers from engaging in behavior that limits private insurance options for particular population groups, such as college students [1] or older persons?
    - How does the PPACA affect the use, and particularly the waiting times, in hospital emergency departments? [2]
    - Under the PPACA, how many consumers had to involuntary change their health care providers or insurers? [4]
    - How does the PPACA affect the availability of primary care [10] and specialist physicians? For example, to what extent does the PPACA motivate physicians to leave and/or amend their participation in public insurance programs in favor of establishing "concierge" business models of medical practice? [19]
    - How does the PPACA affect the availability of both institutional and home- and community-based options for long-term care?
    - To the extent that access to health care has become more universally acceptable, has it (contrary to the European experience with universal health benefits) [9] improved the overall national happiness?
- Has Health Care Become More Affordable Under the PPACA?
    - What is the new Act's impact on national spending for health care? How permanent is any spending impact likely to be? What is the budgetary trend? Have total expenditures been reduced, or only shifted from one payer to another in an elaborate and unspoken shell game?
    - How does the Act affect who (for instance, in terms of age groups or income groups) is shouldering the burden for the public sector portion of health care spending?
    - What is the new Act's impact on health care spending by employers? Are any spending reductions real, or have they been achieved by shifting costs elsewhere? Has the PPACA motivated employers to abandon their recent historical role as supplier of health insurance for employees, dependents, and retirees? [11]
    - What is the new Act's impact on health care spending (taking into account health insurance premium contributions, deductibles, and co-payments, as well as out-of-pocket expenditures) by individuals and families? Does the Act limit the range of individuals' choices concerning health care financing, for example by discouraging individuals from utilizing Health Reimbursement

Arrangements (HRAs), Health Savings Accounts (HSAs), and other tools of Consumer-Directed Health Plans? [21]

- What is the new Act's impact on other parts of the national economy? For example, does the Act lead to an increase or decrease in jobs, as employers deal with added costs associated with employing workers? Does the Act encourage workers to retire at younger ages than they would otherwise retire?
- What is the Act's impact on the affordability of both institutional and home- and community-based long term care? Is the CLASS legislation (Community Living Assistance Services and Supports) embedded in section 10801 of the PPACA a panacea for middle class individuals in planning financially for their long-term care futures, or (as it was characterized by Senate Budget Committee Chairman Democrat Kent Conrad) an unsustainable "Ponzi scheme of the first order, the kind of thing that Bernie Madoff would have been proud of"?
- To what extent does the complex regulatory labyrinth entailed in implementing the PPACA contribute to new, financially draining litigation? [14]
- How has the PPACA impacted the role of philanthropic or charity health care in the United States? Has the PPACA made health care philanthropy irrelevant, or has it had the effect of shifting a greater percentage of the total burden to that resource sector?

It is important not only that all of these outcome questions and a great many more be investigated empirically, but that the resulting data is interpreted as fairly and objectively as possible by private sector analysts and government agencies such as the Congressional Budget Office and the Government Accountability Office that are insulated from partisan political pressures. Further, the evidence-based conclusions must be disseminated to the public and policy makers not only through inherently political forums such as Congressional oversight and investigation hearings [20], but also in timely, dispassionate, and honest fashions that will command credibility rather than partisan distrust and disdain. Only if this occurs will research findings serve as a useful instrument in constructing and implementing future policy modifications on an incremental or grand scale.

In formulating the PPACA, architects and advocates of this legislation pointed favorably to, while skeptics warned critically about, the experience of many other nations whose health systems already exemplified some of the most prominent features ultimately embodied in the U.S. health reform law. As the U.S. proceeds with this unprecedented social experiment and researchers compare its actual versus hypothesized impacts, the American experience will both benefit from and offer valuable lessons to the myriad health care systems firmly or precariously in place across the globe.

References

[1] J. Appleby, Colleges say new health law may imperil student policies, Kaiser Health News (August 20, 2010), available at www.kaiserhealthnews.org/stories/2010/August/19/college-health-plans-reform-law
[2] Associated Press, More ERs advertise wait times, *Wall Street Journal* (Aug. 24, 2010), D2.
[3] Blue ribbon commission to balance the federal budget: A brief introduction from the editors, *Esquire* **154** (Aug. 2010), 106–107.
[4] BNA Health Care Daily Report, Aug. 27, 2010, available at http://news/bna.com/hdln/HDLNWB/doc_display.adp
[5] R.B. Doherty, The certitudes and uncertainties of health care reform, *Annals of Internal Medicine* **152** (2010), 679–682.
[6] Editorial, The separation of health and state, *Wall Street Journal* **CCLVI** (Apr. 6, 2010).
[7] R.A. Fowler, L.-A. Noyahr, J.D. Thornton et al., An official American Thoracic Society systemic review: The association between health insurance status and access, care delivery, and outcomes for patients who are critically ill, *American Journal of Respiratory and Critical Care Medicine* **181** (2010), 1003–1011.

[8] A. Gawande, Testing, testing, *New Yorker*, Dec. 14, 2009, available at www.newyorker.com
[9] T. Geoghegan, *Were You Born on the Wrong Continent?* New Press, New York, 2010.
[10] J.D. Goodson, Patient protection and affordable care act: Promise and peril for primary care, *Annals of Internal Medicine* **152** (2010), 742–744.
[11] D.A. Hyman, Employment-based health insurance: Is health reform a "game changer?", University of Illinois Law and Economics Research Paper No. LE10–010, available at http://ssrn.com/sol3/papers.cfm?abstract_id=1624311
[12] D. Kindig, J. Mullahy, Comparative effectiveness – of what? Evaluating strategies to improve population health, *Journal of the American Medical Association* **304** (2010), 901–902.
[13] N. Laiteerapong, E.S. Huang, Health care reform and chronic diseases: Anticipating the health consequences, *Journal of the American Medical Association* **304** (2010), 899–900.
[14] C. Levey, Health-care reform could create a litigation explosion, *Wall Street Journal* **CCLVI** (Feb. 11, 2010).
[15] D.F. Martin, M.G. Maguire and S.L. Fine, Identifying and eliminating the roadblocks to comparative-effectiveness research, *New England Journal of Medicine* **363** (2010), 105–107.
[16] B. McCaughey, Medical privacy and Obama care, *Wall Street Journal* **CCLVI** (Apr. 9, 2010).
[17] J.P. Newhouse, Assessing health reform's impact on four key groups of Americans, *Health Affairs* **29** (2010), 1–11.
[18] Public Law No. 111–148, as amended by the Health Care and Education Reconciliation Act of 2010, Public Law No. 111–152.
[19] M. Stillman, Concierge medicine: A "regular" physician's perspective, *Annals of Internal Medicine* **152** (2010), 391–392.
[20] G.-M. Turner, Putting the brakes on Obama care, *Wall Street Journal* **CCLVI** (Aug. 25, 2010), A15.
[21] U.S. Government Accountability Office, Consumer-Directed Health Plans: Health Status, Spending, and Utilization of Enrollees in Plans Based on Health Reimbursement Arrangements, GAO-10–616 (2010).