Breaking the Speed Limit

Updated review of the literature on stimulant substitution treatment for amphetamine users in the UK

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'Substitution for Methamphetamine Users – Good Practice from Abroad'

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Presentation structure

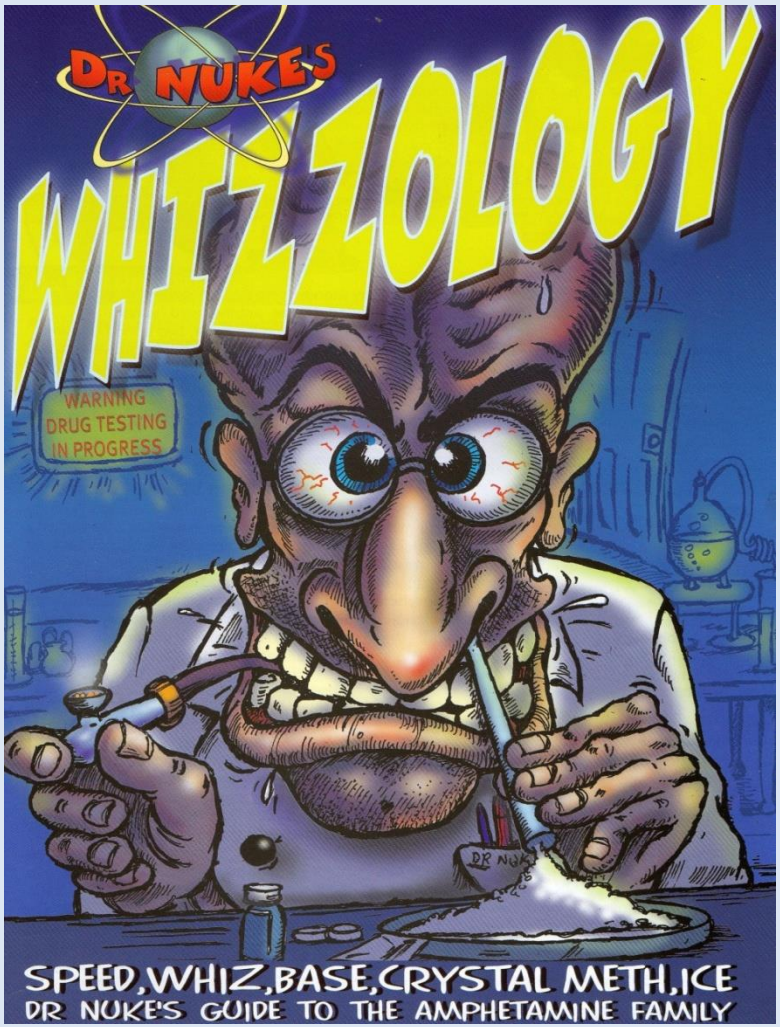
1 Amphetamines in the UK

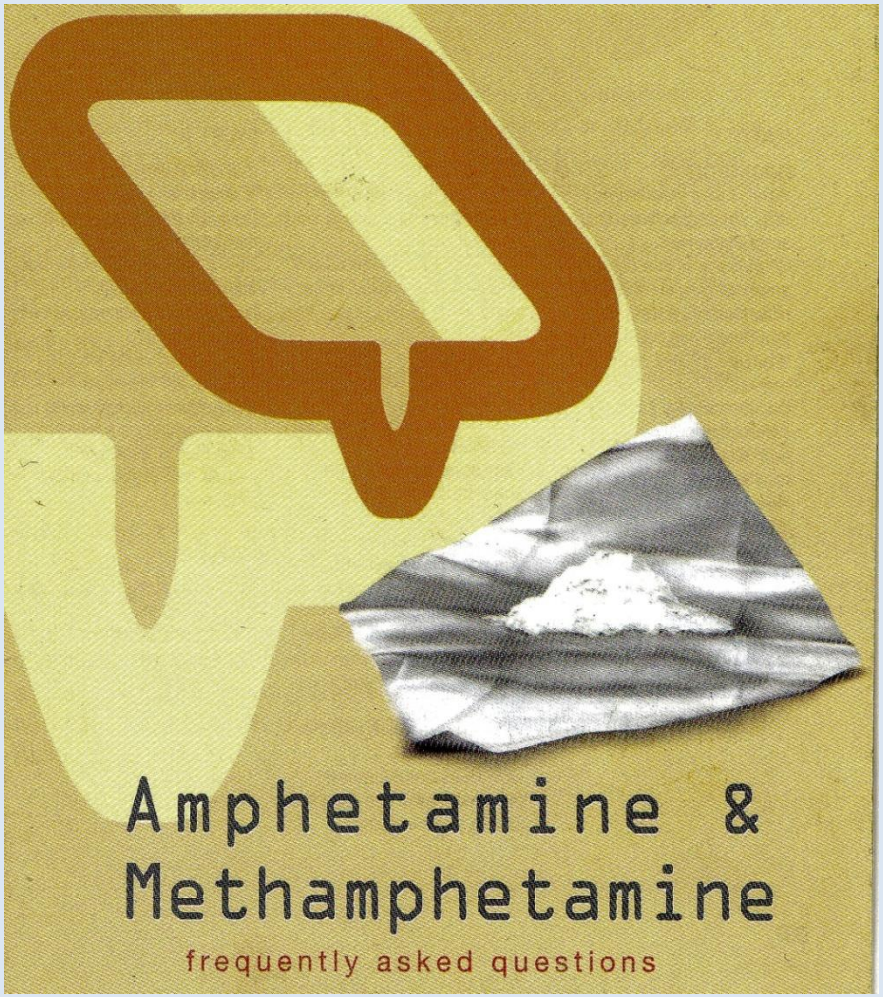
2 International evidence on SST

3 Review of evidence about SST in the UK

4 Conclusions

1. Amphetamines in the UK





Illicit amphetamines in UK

AMPHETAMINE

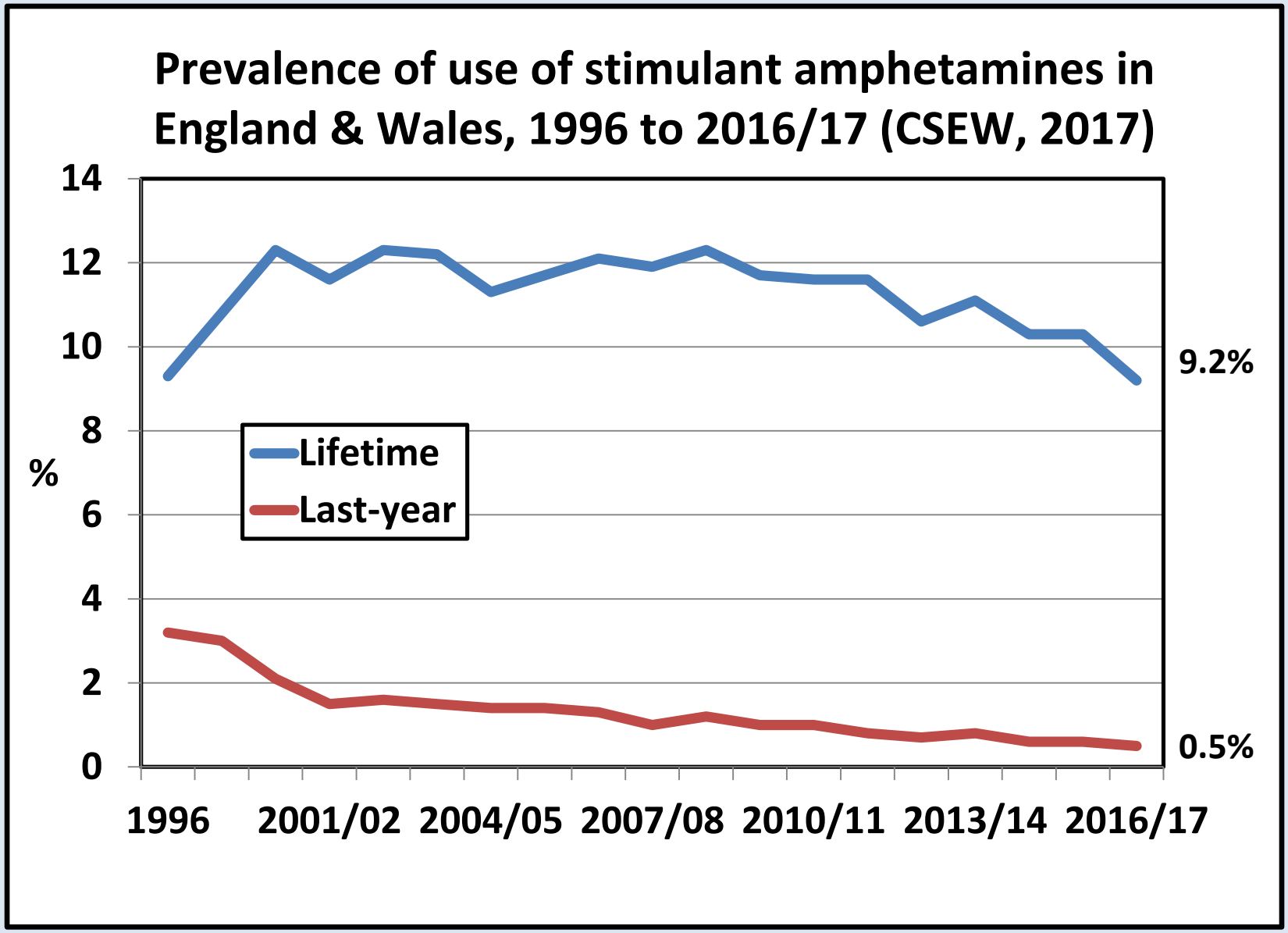
racemic amphetamine sulphate

2 forms: powder - *speed/whizz* (£10 a gram, 5%-10% pure)
paste - *paste/base* (£20 a gram, 15-20% pure).

METHAMPHETAMINE

methylamphetamine hydrochloride / crystal

2 types: powder (*meth*) { both are rare - about £25-£50
crystal (*ice*) { a gram, usually high purity (50%+)


Prevalence of use of stimulant amphetamines in England & Wales, 1996 to 2016/17 (CSEW, 2017)
14
12
10
8
6
4
2
0
%
Lifetime
Last-year
9.2%
0.5%
1996
2001/02
2004/05
2007/08
2010/11
2013/14
2016/17

Amphetamine use, CSEW 2016-17

Use of controlled drugs: amphetamine use ranks 3rd for lifetime use (after cannabis and cocaine) and 4th for last-year use (after cannabis, cocaine & ecstasy)

		Amphetamine		Methamphetamine	
	%	16-24	16-59	16-24	16-59
Lifetime use		*5.6*	*9.2*	*0.7*	*0.6*
Last-year use		*1.1*	*0.5*	*<0.1*	*<0.1*

Number of last-year users (16-59s):		Dependent
Amphetamine	153,000	~3 in 10
Methamphetamine	16,000	NK

~Estimated number of dependent amphetamine users (Adult Psychiatric Morbidity Survey 2014, 16-74s, England): *about* 45,000

Profile of amphetamine users (CSEW)

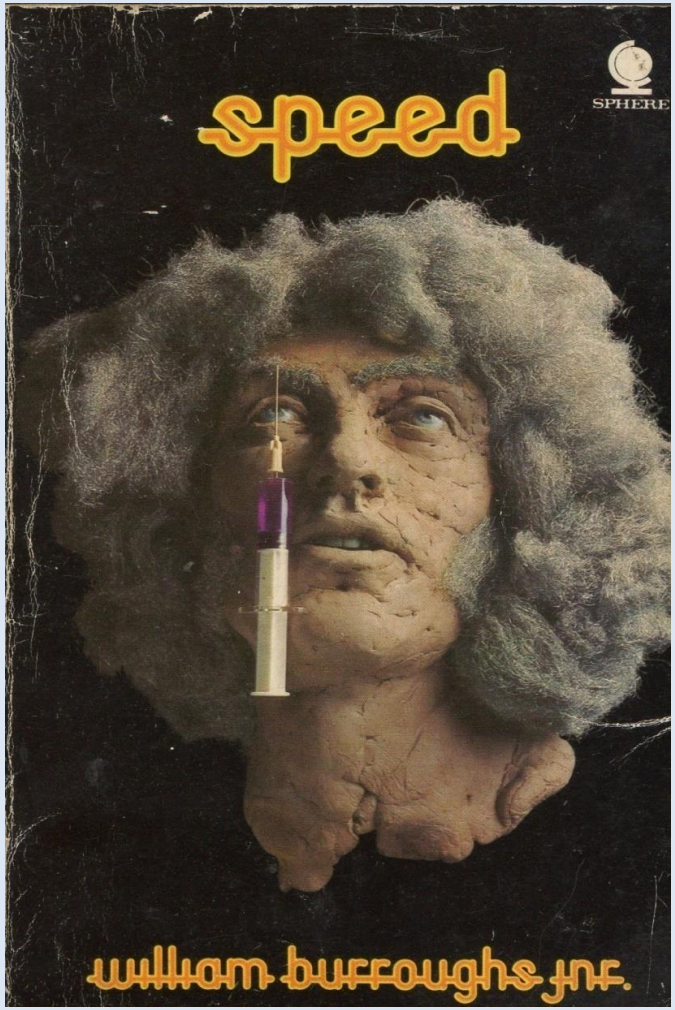
<u>More likely to be</u>:

Young, single, white, male

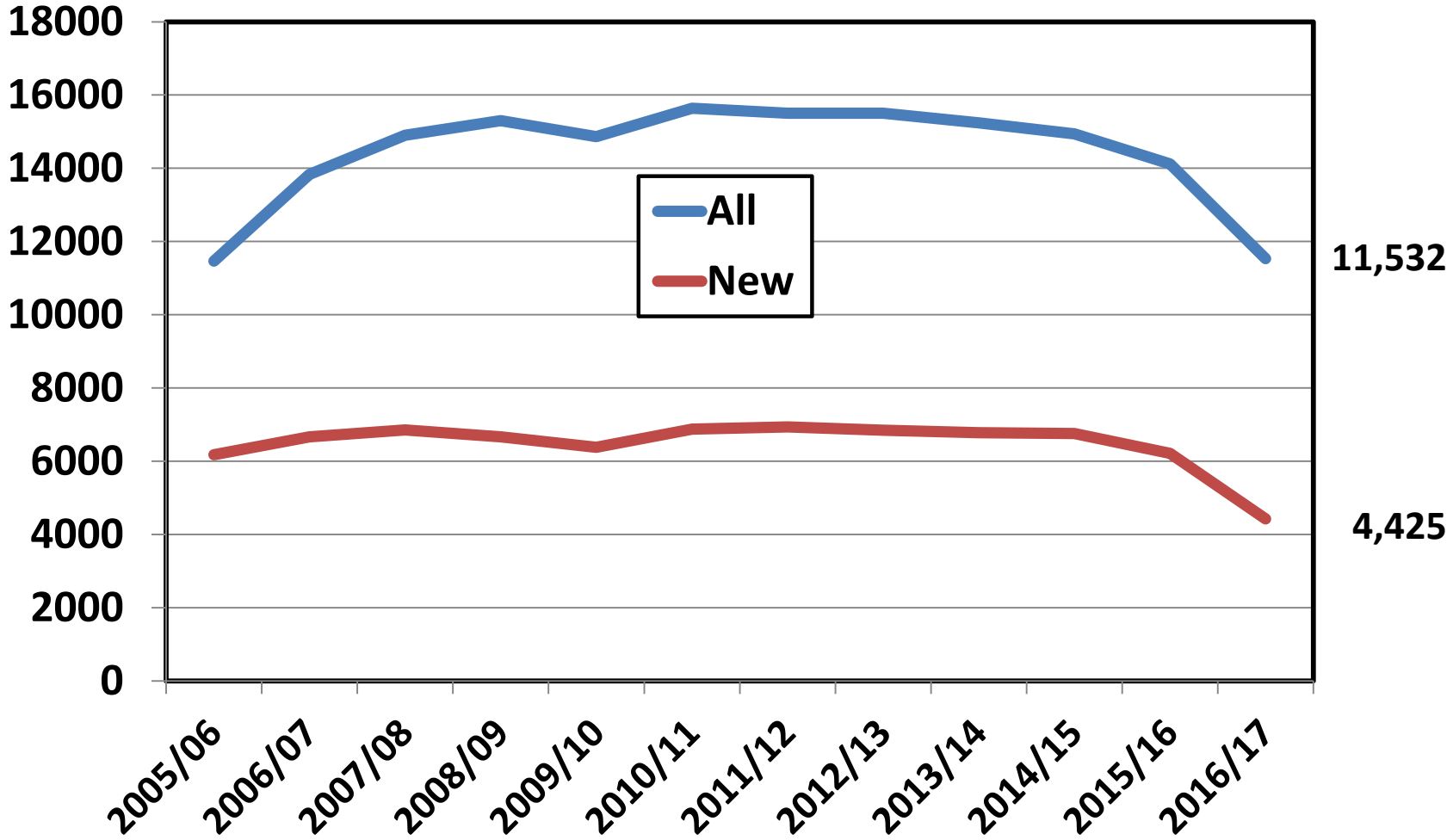
unemployed, lower-income,

multi-drug user,

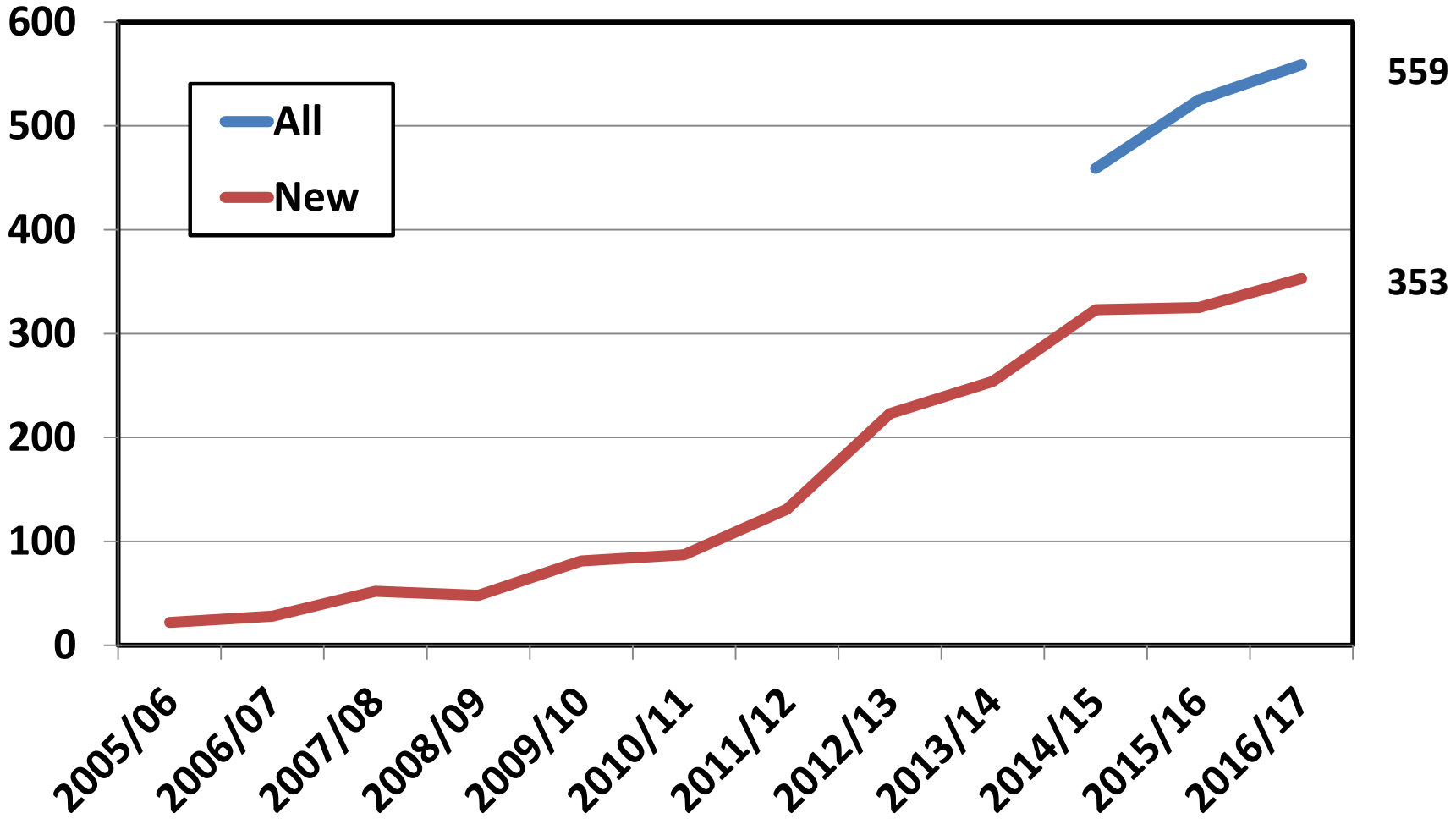
regular bar/club visitor.

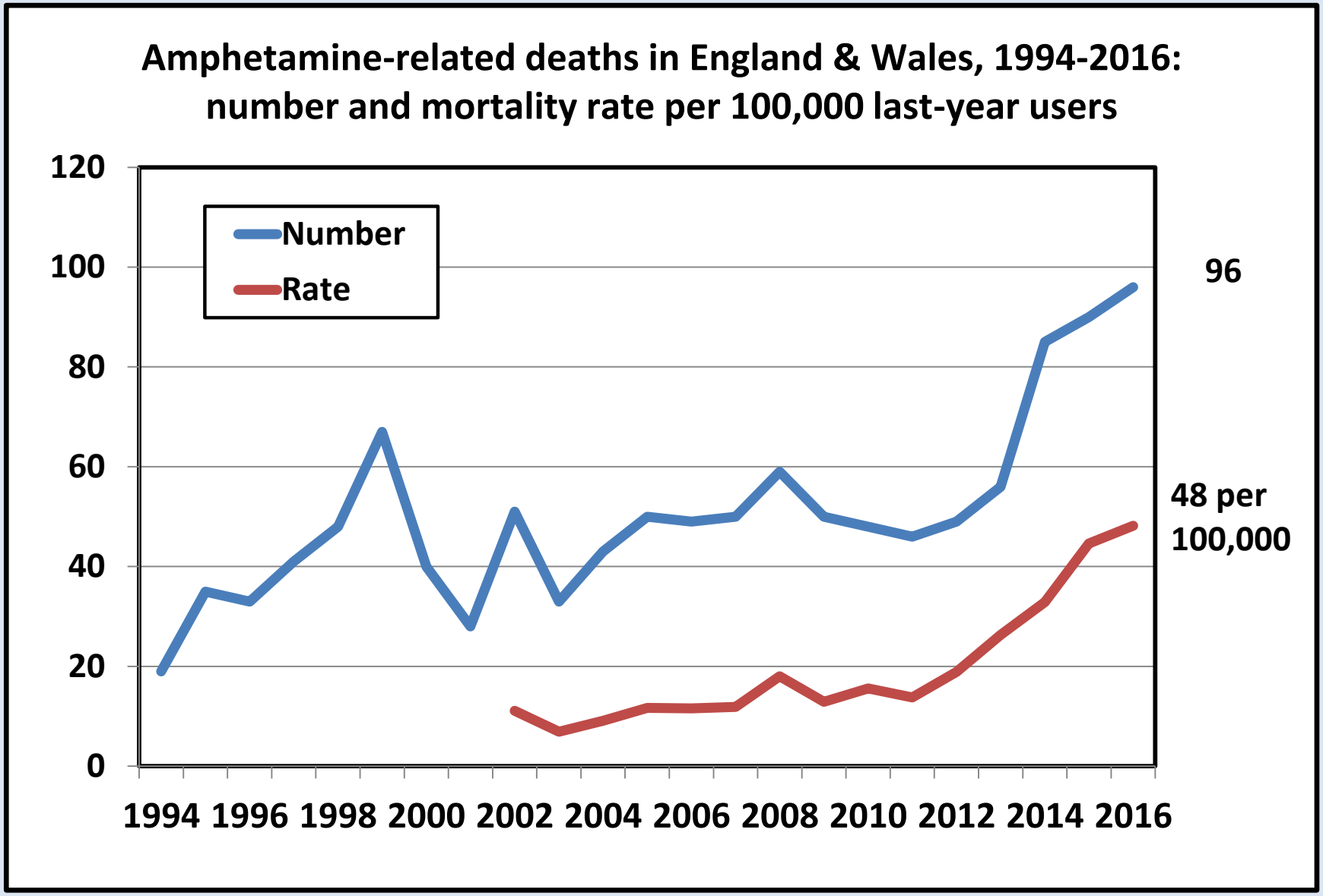


Trends in number of adult amphetamine users in treatment in England, 2005-06 to 2016-17



Trends in number of adult methamphetamine users in treatment in England, 2005-06 to 2016-17

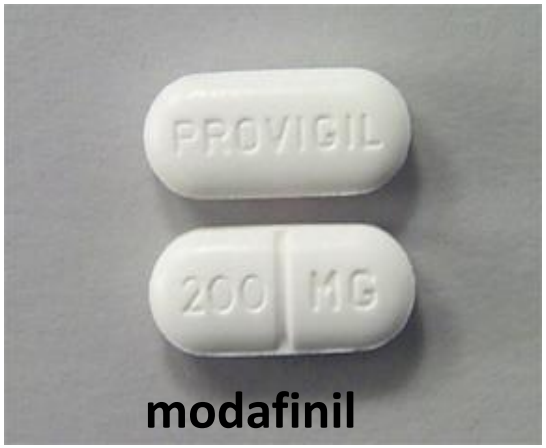



Amphetamine-related deaths in England & Wales, 1994-2016:
number and mortality rate per 100,000 last-year users
120
100
80
60
40
20
0
Number
Rate
96
48 per
100,000
1994 1996 1998 2000 2002 2004 2006 2008 2010 2012 2014 2016

Stimulant prescribing in England

methylphenidate

lisdexamfetamine



modafinil

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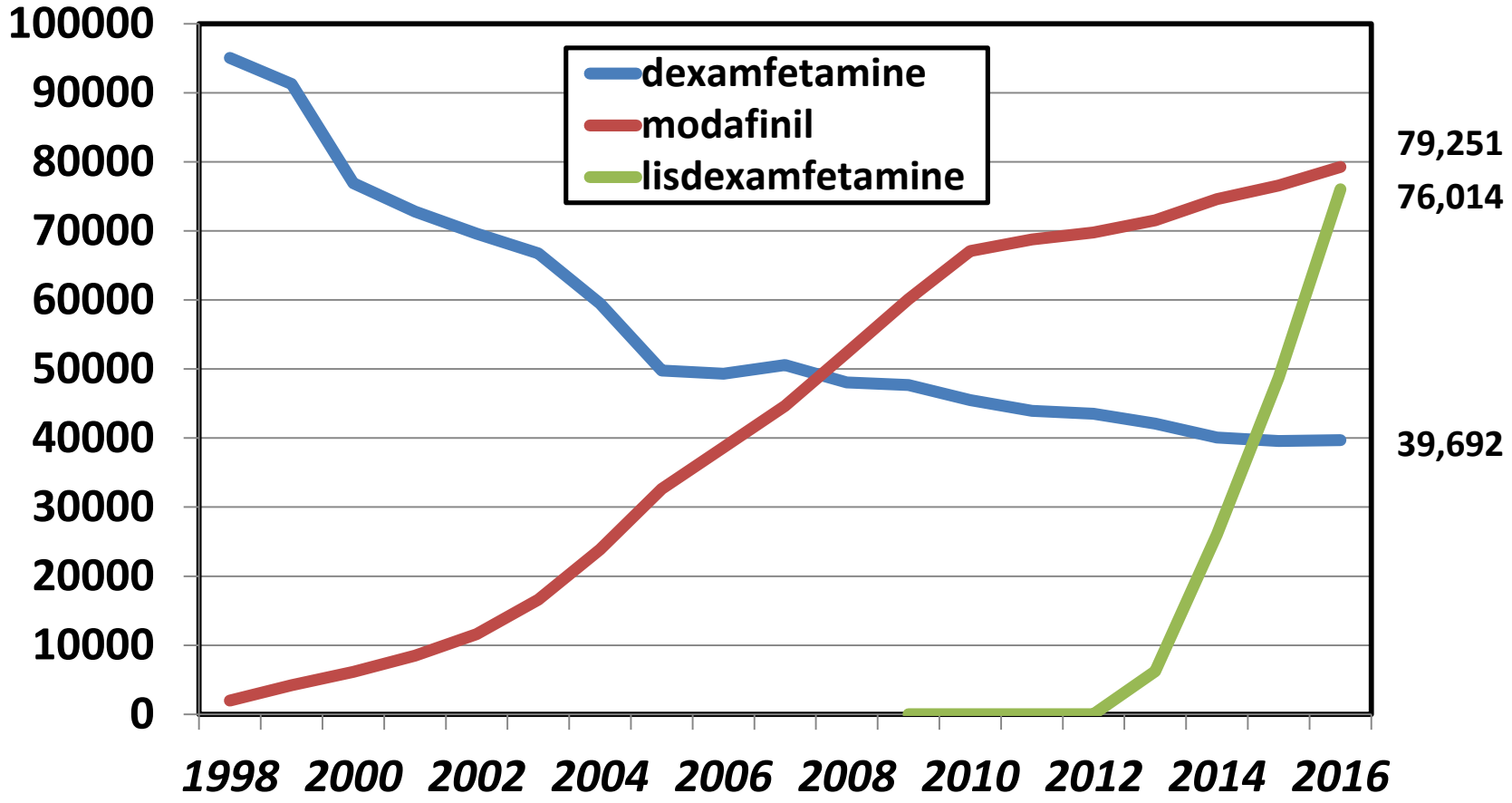
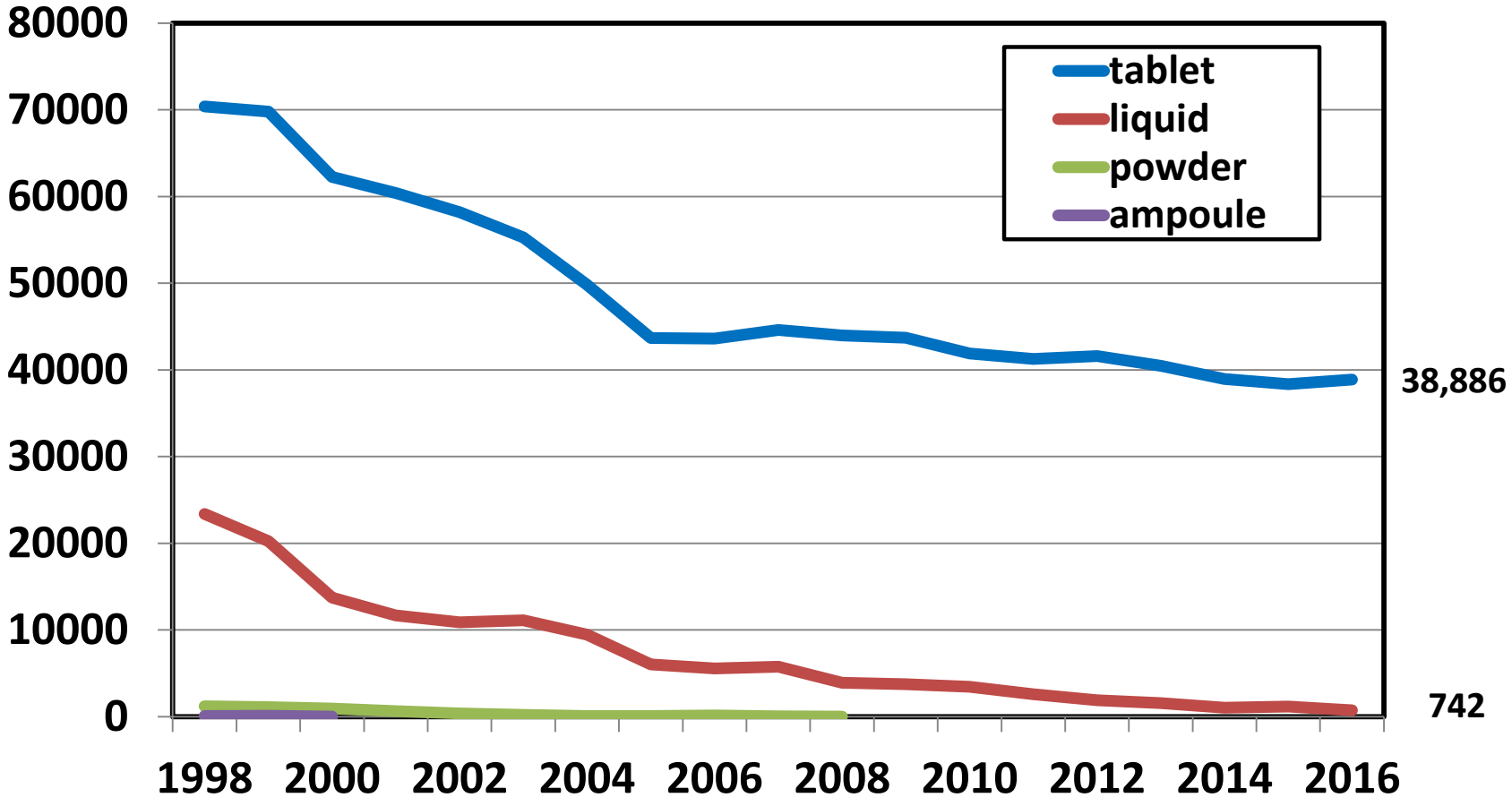
Trends in the number of stimulants dispensed from community pharmacies in England, 1998 to 2016

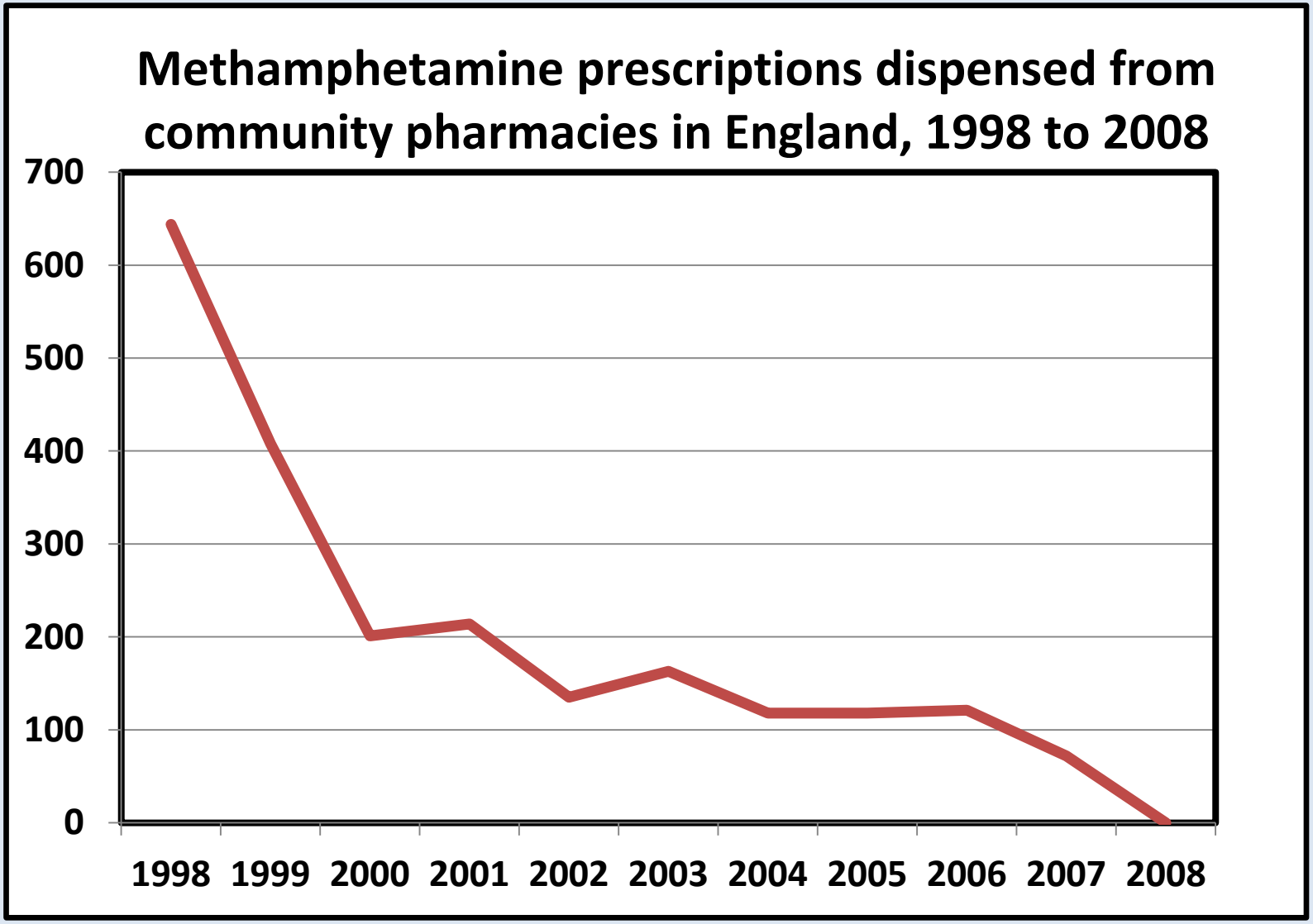


methylphenidate – *1998*: 126,587 *2016*: 1,042,648

Trends in 4 forms of dexamfetamine script dispensed from community pharmacies in England, 1998 to 2016



Adderall capsules - 1998: 0 2016: 64



Methamphetamine was moved from class B to class A of MoDA in 2007

2. International evidence on stimulant substitution treatment (SST)

Conclusions of main reviews

Herin et al. 2010: ‘expanding literature supports use of agonist-like medications to treat stimulant abuse/dependence’.

Brensilver et al. 2013: ‘clinical trials yielded no broadly effective pharmacotherapy’ but ‘promising signals observed for methylphenidate, bupropion etc. … in reducing amphetamine use’

Pérez-Mañá et al. 2013: Cochrane review of 11 randomised, placebo-based, clinical trials found no support for SST for MA users, but based on few studies & missing data (*eg* dose)

Stoop & Rush (2013): ‘dopamine releasers most effective for reducing cocaine use [amphetamines, modafinil] whereas dopamine reuptake inhibitors appear most effective for reducing amphetamine use [methylphenidate , bupropion]’

Longo M et al. (2010). Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. *Addiction*, 105, 146-54.

Longo et al. (2010): RCT study of 49 Australian methamphetamine injectors compared 23 receiving a daily dose of sustained release of up to 110 mg dexamphetamine for 12 weeks (with reducing dose over another 4 weeks) with 26 in placebo condition.

Significant differences found between SST and placebo groups in:

> mean retention in treatment (86 days in SST *vs* 49 days in placebo)

> self-reported methamphetamine use (larger reduction in SST group)

> no serious adverse events in SST group.

Conclusion: "a maintenance pharmacotherapy programme of daily sustained release amphetamine dispensing under pharmacist supervision is both feasible and safe", and "may be an efficacious treatment option for methamphetamine dependence".

3. Review of evidence about stimulant substitution treatment in UK

Drug misuse and dependence

UK Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group

4.10.2.4 Stimulants - substitute prescribing *[same as in 2007]*

"There is no indication for the prescription of cocaine or amfetamines in the treatment of stimulant withdrawal and it is not recommended that other stimulants, such as methylphenidate or phentermine, are prescribed … There was previously thought to be a limited place for the prescription of dexamfetamine in the treatment of amphetamine misuse, and this still occurs in some parts of the UK. The evidence comes from reports that are typically small in number and weak in design, and the evidence of benefit is not convincing. Even though there may be individual patients for whom existing treatment should be continued for the time being, substitute stimulant prescribing should not ordinarily be provided".

"The mainstay of initial and ongoing treatment for problems with [stimulants] is abstinence-oriented psychosocial interventions" p70

21 studies of SST in UK, 1989 to 2007

2 national surveys of prescribing to drug users in England & Wales: pharmacists (1995) & drug treatment doctors (1996)

2 regional studies: 20 DDUs in Midlands, 2000 *(descriptive)*

16 DDUs in North West, 2001 *(experimental)*

Local research: 17 city/county-level reports:

- **4 descriptive**
- **9 were quasi-experimental (compared pre-treatment and post-treatment)**
- **4 were experimental (compared SST with control group)**

No official statistics are available on annual number of drug treatment clients prescribed substitute drugs such as dexamfetamine.

Survey of doctors specialising in drug dependence in England & Wales in 1996

Bradbeer et al. (1998) surveyed 201 medical specialists in drug dependence: 74% response rate = 149 specialist doctors

* **46% prescribed amfetamines to drug users – among whom**
  (a) 62% put no limit on duration of prescribing, and
  (b) mean maximum daily dose was 66 mg dexamfetamine.

* **60% saw a role for dexamfetamine (DA) prescribing**
* **32% of doctors who did not prescribe amfetamines stated that they would like to do so**

Survey of community pharmacy services for drug misusers in England & Wales 1995

1 in 4 sample of 10,600 (75% response rate) = 1,984 pharmacies

Strang & Sheridan (1997): after methadone (92%), amfetamines were the 2nd most commonly prescribed controlled drug (4%) - dispensed by 1 in 20 pharmacies

Type: Dexamfetamine tabs (73%) & liquid (24%) - 44 mg/day
Dex/meth-amfetamine ampoules (3%) - 50 mg per day

Typical dispensing interval: once a week to once a month

It was estimated that 900-1,000 drug users were prescribed amfetamines in England & Wales in 1995

3D Research estimate for 2017: ~200

Multi-agency study of dexamfetamine prescribing in NW England (Klee et al. 2001)

Design: based on 16 drug clinics & 3-month study period

Recruited three samples of amphetamine users:

1. **users in community/no treatment (n = 43)** **NT**
2. **users in prescribed dexamfetamine treatment (n = 28)** **DT**
3. **users in other treatment/not prescribed dex. (n = 30)** **OT**

Three matched samples of 16 amphetamine users compared.

Findings

1. **DTs more likely than OTs to be retained in treatment**
2. **Only DTs showed a steady drop in the amount and frequency of amphetamine use – and were more likely to cease using/injecting (1 in 3) compared with OTs (zero)**
3. **DTs who got counselling had greater health improvement**

Location of researched treatment agencies prescribing amfetamines to drug users in England &Wales, 1984 to 2009

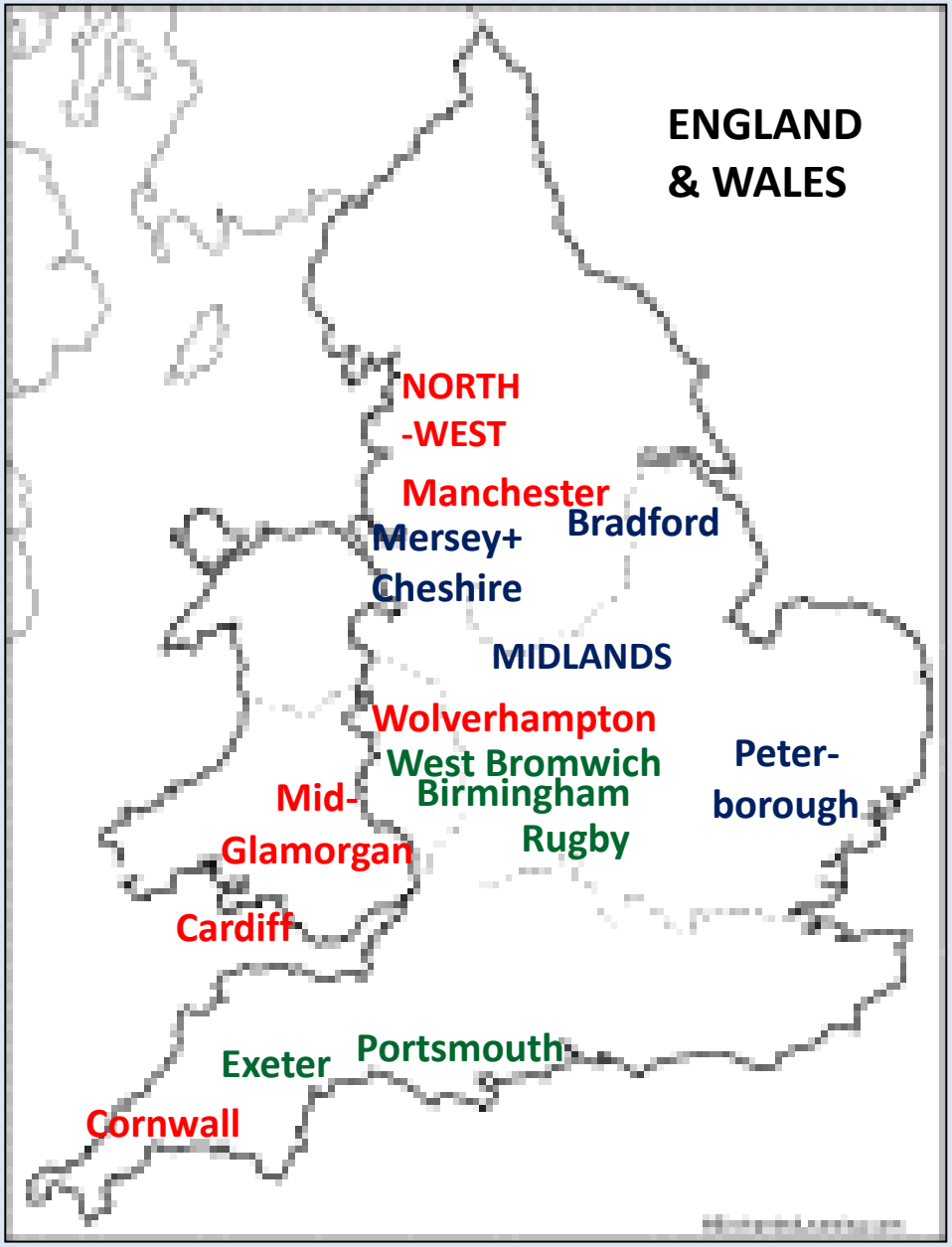
Experimental (controls: in treatment but no dexamfet. prescription *or* drop-outs *or* never had treatment)

Quasi: pre/post treat. comparison

Descriptive study

Small case: cities/towns/counties
LARGE CASE: regions (no. agencies):
North-West (16), Midlands (19)

Some of these treatment agencies have now ceased/reduced prescribing of amfetamines to *speed* users.



Summary of methods of 13 local comparative studies of SST in England & Wales

	First author /year	Location	Sample	Comparison .
1	Kahn (1989)	Birmingham	67	* Pre+Post Treat.
2	Willoughby (1989)	Exeter	29	Pre+Post Treat.
3	Rugby CDT (1993)	Rugby	35	* Pre+Post Treat.
4	Pates (1994, 1996)	Cardiff	10	Pre+Post Treat.
5	McBride (1997)	Glamorgan	63 [25]	Experi-Control
6	Fleming (1994/98)	Portsmouth	?	Pre+Post Treat.
7	Charnaud (1998)	Cornwall	60	Pre+Post Treat.
8	White (2000)	Cornwall	148	Pre+Post Treat.
9	Carnwath (2002)	Manchester	8	Pre+Post Treat.
10	Myton (2004)	Wolverhampton	20	Experi-Control
11	Merrill (2004)	Manch./Cardiff	30 [30]	~ Experi-Control
12	White (2006)	Cornwall	47 [41]	Experi-Control
13	Rasheed (2007)	W. Bromwich	56/32	Pre/Post Treat.

[ ] control group * methamphetamine prescribing ~ RCT

Methodological problems

In-house rather than independent evaluations

Small or unrepresentative samples

Short assessment and monitoring periods

Lack of control/comparison groups, and only one RCT

Self-reported behaviour, with few validity checks

Patchy coverage of relevant outcome variables

Limited statistical analyses

‘Dexamphetamine Substitution as a Treatment of Amphetamine Dependence: a Two-Centre Randomised Controlled Trial’

Sample: 59 treatment clients meeting DSM IV criteria for amphetamine dependence were recruited from 2 centres in Manchester and Cardiff - 32 were randomly allocated to DEX and 27 to BATA.

DEX: maintenance dexamfetamine prescribing over first 4 months - up to 100 mg per day, dispensed daily at community pharmacy - then gradually withdrawn over the next 3 months

BATA: best available treatment alone (advice, harm reduction, etc.)

Research interviews: (1) early outcome, based on months 1 and 4, *vs* (2) later outcome (withdrawal phase), based on month 7 (end of treatment) and month 9 (2 months after end of treatment)

Weekly clinical monitoring data: first 4 months *vs* months 5 to 7.

Source: Merrill J et al. (2004). Report to Department of Health.

Findings of RCT in Manchester & Cardiff

On entry: 71% male, 56% injecting, mean last-week use: 19.3 grams
Median attendance at 16 clinic appointments: DEX: 7 BATA: 5
No adverse effects in either group on physical and mental health.
Illicit amphetamine use and injecting: no significant differences

<u>Significant differences between DEX and BATA</u>

Poly-drug use: reduction in later outcome (withdrawal) phase
Physical health: improvements in early (maintenance) phase
Mental health: improvements in early and later phases
Body weight: reduced in early phase, increased in later phase

<u>Conclusion</u>: "the study provides modest support for the benefits of prescribing dexamphetamine … dexamphetamine substitution should remain a specialist treatment intervention carried out by experienced practitioners"

<u>Criticism</u>: period too short for producing and monitoring some effects

Outcome variables assessed by 13 local experimental studies of SST in England & Wales

Client Contact > Service Delivery > Risk-Reduction (Behaviour-Change) > Harm-Reduction (Consequences)

Contact: making contact (M) & retention/drop-outs (R)

Delivery: proper prescription-use (P), general compliance (C), needle exchange (X), counselling (Cg), other services (O)

Risk-reduction: amphetamine use (A), other drug use (D), injecting (I), needle-sharing (N), amount used (Am), frequency (F)

Harm-reduction: physical health (Ph), mental health (Mh), dependence (Dp), acquisitive crime (Ac), violent crime (Vc), social problems (Sp), unsafe sex (Us), blood-borne viruses (Bv), death (De), costs (C)

Summary of outcomes of 13 local studies of amfetamine prescribing in England & Wales

	Contact	Delivery	Risk-Reduction	Harm-Reduction
1	R		I	Ac
2			I	Mh Us
3			A N	Mh Ac
4			I Am	Ac Ph Us
5	M R		I N Am F D	
6	M		A I N D	Ac
7			I	
8			A I	Mh
9		C		Mh
10			A I	Ph Sp
11			D	Ph Mh
12		C		
13	R			Mh

Key positive outcomes from local experimental studies of SST in England & Wales

1. SST attracts and retains clients in treatment
2. Effective at service delivery and uptake (notably compliance with regulations, no script diversion)
3. Reduces risky/undesirable behaviour - notably use of illicit amphetamine and other drugs, injecting, and needle-sharing
4. Increases positive outcomes, notably improvements in physical and mental health, and reduced acquisitive crime

5. Conclusions

Recommended criteria of inclusion and exclusion for dexamfetamine prescribing based on review of literature

Criteria of inclusion

1. **Primary amphetamine use – injecting & non-injecting**
2. **Heavy use (>50mg per day, most days of week – which is equivalent to >1g per day of illicit *speed* at 5% purity)**
3. **Longer-term use (at least 3 months)**
4. **Dependent use, with escalating craving & withdrawals**

Criteria of exclusion (flexible)

1. **Some kinds of poly-drug use**
2. **Some kinds of mental illness**
3. **Some health problems – esp. heart disease, low weight**
4. **Pregnancy**

Stimulant scripts: key issues for service provision and evaluation

Can effectiveness be improved by tailoring scripts to fit consumption behaviour of each amphetamine user?

Stimulant dexamfetamine, lisdexamfetamine
methamfetamine
methylphenidate, modafinil

Form ampoule, powder, tablet/liquid, reefer/vape

Dose daily maximums: 90 mg dexamfetamine ?
120 mg methamfetamine ?

Dispensing daily *vs* twice-weekly *vs* weekly pick-ups

Overview & Conclusions

1. **Amphetamine is 4th most prevalent drug in UK – though levels of use have dropped off while linked deaths are rising**
2. **Substitute prescribing of dexamfetamine continues to be offered by some treatment agencies, though numbers have dropped significantly in 21st century**
3. **Research from 1989 to 2007 provides enough evidence that SST can be effective to justify continuing with such services and conducting more experimental and evaluation research**
4. **More randomized controlled trials are particularly needed, covering different substitute stimulants in different forms, dose regimes, and dispensing schedules.**

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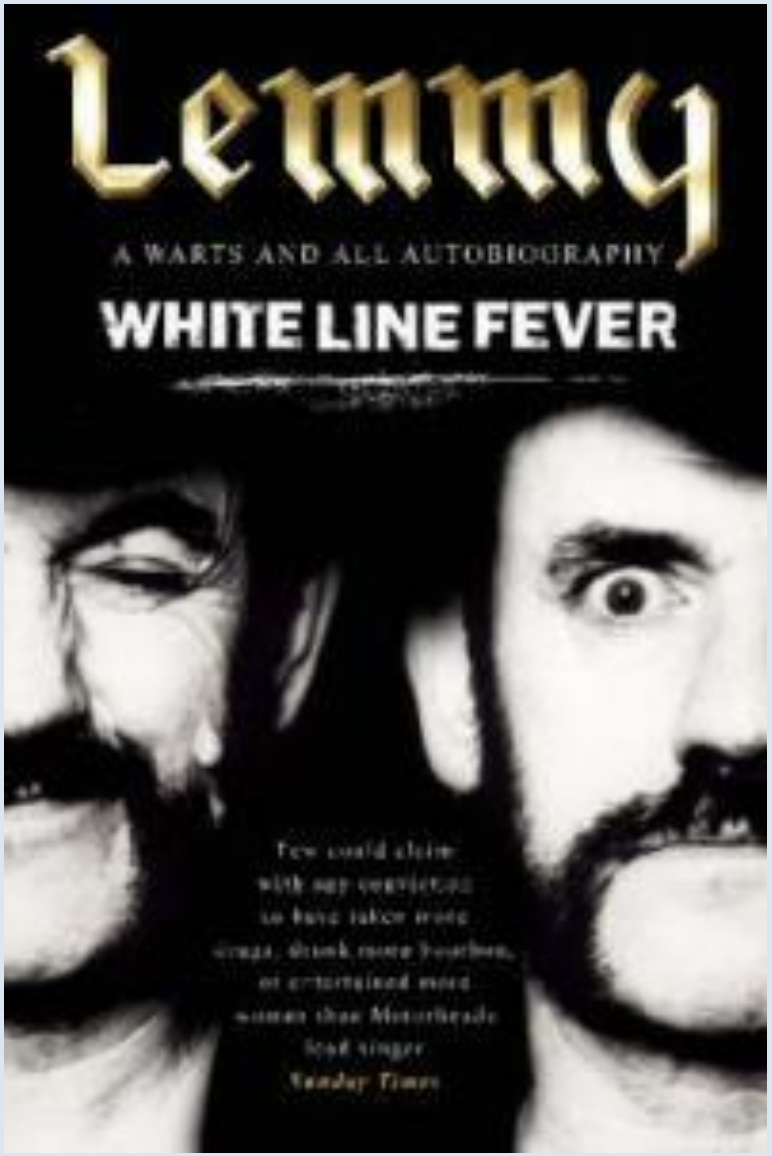

'All scientific work is incomplete... That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time'.
Bradford Hill, UK epidemiologist who researched link between smoking and lung cancer

Appendices

ABSTRACT

Breaking the Speed Limit: Updated review of the literature on stimulant substitution treatment for amphetamine users in UK

This paper reviews the available evidence about the effectiveness of stimulant substitution treatment (SST) for amphetamine users in the UK. Four international reviews of studies of SST have generally concluded that there is evidence of effectiveness on important harm reduction outcomes, and/or that more research is needed, notably regarding the impact of dose. The studies reviewed covered SST with four drugs – methylphenidate, dexamfetamine, modafinil and bupropion – and mostly involved users of methamphetamine, when over 95% of UK *speed* use involves racemic amphetamine sulphate.

Two national surveys have shown that the number of UK services and GPs prescribing stimulants to amphetamine users grew steadily at the end of the 20th century. By the mid-90s, over 100 treatment specialists and 400 pharmacies were involved in SST with about 1,000 amphetamine users. The typical prescription involved a daily dose of 30-60mg of dexamfetamine tablets or liquid, dispensed weekly as a 'take-home script'. However, over the last two decades, dexamfetamine prescribing has notably declined, to an estimated 200 amphetamine users a year. The prevalence of last-year amphetamine use in England & Wales has also dropped over sixfold - from 3.2% in 1996 to 0.5% in 2016/17 - while the number of amphetamine-related deaths has risen fivefold, from 19 in 1994 to 96 in 2016.

A study of 16 North-West treatment agencies involved in SST in 2001 found that over three months following the start of treatment, amphetamine users prescribed dexamfetamine reported significant reductions in risky drug-taking behaviours compared with matched controls – as well as being less likely to 'drop out'. 13 experimental studies of SST have also been provided on over 500 clients of local treatment services in Britain. However, this research is limited and patchy - most notably, there has been only one RCT and three studies with control groups. Nevertheless, it provides consistent supportive evidence of the effectiveness of dexamfetamine prescribing on various indicators of harm reduction, including: making and maintaining contact with amphetamine users; delivering various services; reducing problematic behaviour (notably illicit drug use, injecting and needle-sharing), and, ultimately, reducing harmful outcomes (notably physical health problems, mental disorder, and acquisitive crime). It is concluded that the evidence base is sufficient to justify further exploration of SST by UK drug treatment agencies within guidelines for best practice, including criteria for inclusion (eg. injecting or dependent use, no history of psychosis). Independent and longer-term studies employing control groups - particularly RCTs - are urgently required to assess the effectiveness of SST in achieving harm-reduction outcomes.

Dr Russell Newcombe, 3D Research, Liverpool, UK; March 2018

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DRUGS IN NAZI GERMANY

Norman Ohler

ALLEN LANE
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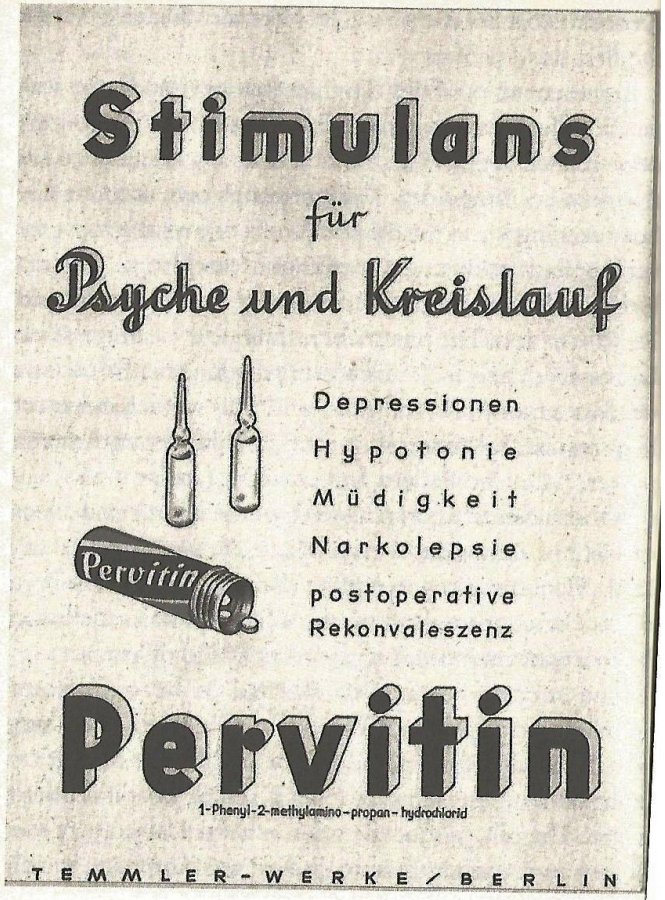

Advertising poster for the supposed panacea.
'Stimulant for psyche and circulation'
'Depression – hypotonia – fatigue – narcolepsy –
post-operative convalescence
Pervitin
1-phenyl-2-methylamino-propane-hydrochloride
Temmler Works, Berlin'