Arzneimittelmissbrauch und Arzneimittelsicherheit – ärztliche Identität im Spannungsfeld gesundheitspolitischer Angstvorstellungen und biotechnokratischer Verheissungen

Prof. Dr. Alfred Springer

18. Substitutionsforum
Schlosshotel Mondsee 18. 04. 2015
Arzneimittelmissbrauch – eine neue Gefahr?
Kapitel 1: Drogenpolitik
4. Enable a more informed response to the challenge of the misuse of prescribed and ‘over the counter’ opioids and other psychoactive medicines.
50. Enhance data collection, research, analysis and reporting on:
   • (a) drug demand reduction;
   • (b) drug supply reduction;
   • (c) emerging trends, such as polydrug use and misuse of prescribed controlled medicines, that pose risks to health and safety;
   • (d) blood-borne viruses associated with drug use including but not limited to HIV and viral hepatitis, as well as sexually transmittable diseases and tuberculosis;
   • (e) psychiatric and physical co-morbidity;
   • (f) drug problems among prisoners and the availability and coverage of drug demand reduction interventions and services in prison settings; and
   • (g) other drug-related consequences
• Im Bereich Demand reduction gibt der Plan folgerichtig gleich als erste Aufgabe Aktionen vor, die das Problem des Missbrauchs von verschriebenen Arzneimitteln und von nicht verschreibungspflichtigen Mitteln in Angriff nehmen.
Europäische Commission: neue Aufgabenstellungen

• Auch von der Europäischen Kommission wird vermerkt, dass die Europäische Drogenpolitik neue Herausforderungen anspricht, wie etwa den zunehmenden Trend zu Mischgebrauch (einschliesslich Kombinationen von erlaubten Substanzen wie Alkohol und kontrolllierten Arzneimitteln und verbotenen Substanzen)........

• Der Plan wurde während der Irischen Päsidentschaft fomuliert, die Umsetzung wurde zur Aufgabe der Litauischen Präsidentschaftsperiode.
<table>
<thead>
<tr>
<th>Irland: Januar - Juni 2013</th>
<th>Litauen: Juli - Dezember 2013</th>
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<tr>
<td>Griechenland: Januar - Juni 2014</td>
<td>Italien: Juli - Dezember 2014</td>
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<td>Lettland: Januar - Juni 2015</td>
<td>Luxemburg: Juli - Dezember 2015</td>
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<td>Malta: Januar - Juni 2017</td>
<td>Vereinigtes Königreich: Juli - Dezember 2017</td>
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<td>Estland: Januar - Juni 2018</td>
<td>Bulgarien: Juli - Dezember 2018</td>
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<tr>
<td>Österreich: Januar - Juni 2019</td>
<td>Rumänien: Juli - Dezember 2019</td>
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Priorities of the LT HDG Presidency:

- New Psychoactive Substances
- Misuse of Prescribed Medicines
- 2014 CND and UNGASS 2016
- Drug Supply Indicators
- Dialogues with the Third Parties
MISUSE OF PRESCRIBED MEDICINES

**Why Misuse of Prescribed Medicines:**

- EU Drugs Strategy - one of the new challenges and priorities in the field of drug demand reduction
- EU Action Plan on Drugs (2013-2016) - responsible parties to enable a more informed response to the challenge
- The real scale of misuse of prescribed controlled medicines in the EU is unknown
- Misuse of prescribed controlled medicines - a real and current problem across the EU Member States
- Challenges on population health, social cohesion and economy and on health system capacity
Die Begründung der Setzung des Schwerpunkts

LITHUANIAN ACHIEVEMENTS IN THE FIELD OF MISUSE OF PRESCRIBED MEDICINES

European Drug Report 2014

Opioids other than heroin: of increasing concern

In 2012, in the majority of European countries (17) more than 10% of first-time opioid clients entering specialised treatment were misusing opioids other than heroin (Figure 2.9). These included methadone, buprenorphine and fentanyl. In some countries, these drugs now represent the most common form of opioid use. In Estonia,
THE AIM OF LITHUANIAN PRESIDENCY

To achieve a **balance** between the **availability** of prescribed medicines and their **abuse**, noting that the **access to medicines should not be restricted** by "the fear of enabling" misuse.
MISUSE OF PRESCRIBED MEDICINES

Main problems:

- balances that need to be struck when addressing dependence on prescribed medicines

- lack of appropriate and adequate pain management because of the fear of misuse and dependence

- shortage of appropriate and wide access to OST because of exhaustive control prerequisites

- you cannot prevent a “public health crisis” in the making, if you do not take early steps to identify and address potential risks
Areas of focus:

- Raising awareness of the risks and consequences
- Misuse of prescribed and "over the counter" opioids
- Comprehensive and integrated treatment services (including those which address polydrug use)
- Health care measures for drug users in prison and after release
- Minimum quality standards of drug demand reduction
Running the discussion on EU level:

- Global Addiction Conference in Rome in June 2014 – a special session on Dependence on prescribed medicines
- One of the main priorities for Italian EU Presidency
- International Conference in Vilnius in November 2014 - a workshop on Misuse of Prescribed Medicines
17 July 2013, erstes Treffen der Horizontal Drugs Group (HDG) unter der Präsidentschaft Litauens
<table>
<thead>
<tr>
<th>From:</th>
<th>Presidency</th>
</tr>
</thead>
<tbody>
<tr>
<td>To:</td>
<td>Horizontal Working Party on Drugs</td>
</tr>
<tr>
<td>Subject:</td>
<td>Misuse of and dependence on prescribed medicines in the European Union: setting a common definition and indicators for monitoring</td>
</tr>
</tbody>
</table>

Brussels, 8 September 2014
European Council, Brussels, 23 October 2014

• Tagung: “Misuse of and dependence on prescribed medicines: defining the scope of the problem”
EU Drug Control Policymaking and Implementing: Role of the EU Member State

International Conference
“Reducing the demand for drugs – improving human life”
11-12 September 2014, Kiev
Hintergrundinformation
ALICE RAP Policy Paper Series

Policy Brief 4.

Prescription opioids and public health in the European Union
Schlussfolgerung

• Obwohl die Dimension des Problems in keinem Europäischen Land mit den US-Verhältnissen verglichen werden könne, nimmt offenkundig die Abgabe der Substanzen zu und man muss daher den Bezug zu negativen Konsequenzen im Auge behalten. Man dürfe es nicht riskieren, dass mit den USA vergleichbare Verhältnisse hinsichtlich der Überdosis-Mortalität entstehen.
EMCDDA award 2014 goes to ALICE RAP paper

• The visiting research fellows Ludwig Kraus and Robin Room at Centre for Social Research on Alcohol and Drugs (SoRAD), along with ten other European scientists working in the EC-funded ALICE RAP project were awarded a prestigious EMCDDA 2014 Scientific Paper Prize. The EMCDDA Scientific Paper award was inaugurated in 2011 by the EMCDDA Scientific Committee. It celebrates scientific writing and distinguishes high-quality research in the field of illicit drugs.

• The ALICE RAP project (Addiction and Lifestyles in Contemporary Europe – Reframing Addictions Project) brings together a network of over 150 researchers who study many different aspects of addiction from a wide range of different disciplines.
Kapitel 2: Epidemiologisches
Weltweite Zunahme des Opioidverbrauches 1988-2007
Opioidverbrauch (kg/Mio Einwohner) Europa 2002 und Morphinverbrauch (kg) Welt 2007

kg / Millionen Einwohner

- Dänemark 70
- Großbritannien 47
- Schweden 35
- Frankreich 32
- Irland 29
- Norwegen 27
- Österreich 21
- Schweiz 20
- Deutschland 18
- Niederlande 10
- Griechenland 9
- Italien 3
- Spanien 1

Pie Chart:
- United States (4.9%)
- Others (60.8%)
- Japan (2.1%)
- Canada (0.6%)
- Australia and New Zealand (0.4%)
- Europe (11.2%) 24.2%
- Japan (2.1%) 1.0%
- Others (60.8%) 7.4%
- United States (4.9%) 59.7%
### Tabelle 1

**Behandlungsprävalenz (%) mit Opioiden**

<table>
<thead>
<tr>
<th>Jahr</th>
<th>des Vorjahres</th>
<th>1999</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Männer</td>
<td>Frauen</td>
</tr>
</tbody>
</table>

**Veränderungen (Δ) 2000 zu 2010:**
- Männer: +37,3 %
- Frauen: +37,1 %
- Gesamt: +37,0 %

**Veränderungen (Δ) 1999 zu 2010:**
- Männer: +18,6 %
- Frauen: +24,3 %
- Gesamt: +22,0 %
Kernaussagen

- Es gibt einen deutlichen Trend zur Verordnung von WHO-3-Opioiden, insbesondere bei Nichttumorpatienten.
- Auch die Verordnung von nichtretardierten Zubereitungsformen hochpotenter Opiode (WHO-Stufe 3) nimmt zu.
- Der überwiegende Anteil der Opioid-Verordnungen erfolgt für Nichttumorpatienten.
- Die Anzahl der Langzeitbehandlungen mit Opioiden bei Nichttumorerkrankung steigt trotz unzureichender Evidenz an.
Exkurs USA
US-Statistik

Popping Pills - A Drug Abuse Epidemic

52 Million People in the US over the age of 12 have used prescription drugs non-medically in their lifetime (NDA 2011)
Missbrauch von Arzneimitteln als zunehmendes Problem

A Flood of Opioids, a Rising Tide of Deaths
Susan Okie, M.D.

Faced with an epidemic of drug abuse and overdose deaths involving prescription opioid pain relievers, the Food and Drug Administration (FDA) plans to require opioid makers to provide training for physicians and patient-education materials on the appropriate prescribing and use of extended-release and long-acting versions of these drugs. But since July, FDA officials have been scrambling to revise their proposed Risk Evaluation and Mitigation Strategy (REMS), after an advisory panel (the agency’s Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee) voted 25 to 10 against the FDA’s plan, saying it didn’t go far enough. Advisors urged that training in appropriate use of opioids be made mandatory for all physicians who prescribe them.

In the eyes of many patients, these opioids “are essentially legal heroin,” advisory committee member Lewis Nelson of New York University School of Medicine commented during the panel’s discussion. “We need to think about how we would construct a REMS if we were going to be marketing heroin.” With more than a million prescribers of controlled substances registered with the Drug Enforcement Administration (DEA) and about 4 million U.S. patients receiving long-acting or extended-release opioids each year, the FDA’s opioid REMS will affect far more people than any existing REMS for high-risk medications. Any discussion of restricting the use of pain medicines provokes emotional debate, with some advocates warning that people in chronic pain may be undertreated or stigmatized and others arguing that access to powerful painkillers leads to thousands of deaths each year.

There is ample evidence that action is needed. According to the Centers for Disease Control and Prevention (CDC), deaths from unintentional drug overdoses in the United States have been rising steeply since the early 1990s (see bar graph) and are the second-leading cause of accidental death, with 27,658 such deaths recorded in 2007. That increase has been propelled by a rising number of overdoses of opioids (synthetic versions of opium), which caused 11,499 of the deaths in 2007 — more than heroin and cocaine combined (see line graph). Visits to emergency departments for opioid abuse more than doubled between 2004 and 2008, and admissions to substance-abuse treatment programs increased by 400% between 1998 and 2008, with prescription painkillers being the second most prevalent...
USA: Verordneter Opioidverbrauch 1997-2007

grafische Darstellung der Verordnung von Opioiden in den USA von 1997 bis 2007

- Oxycodone
- Hydrocodone
- Morphin
- Methadon

Pharmazeutische Gesellschaft Zürich / ETH
30. Januar 2014

Trescot AM, Pain Physician 2008;11:S5-S62
USA: Opioidmissbrauch vs. Opioidverordnungen

Opioidmissbrauch = Problem der jungen Menschen
* Data for ED visits involving adverse reactions to pharmaceuticals are not available for 2004.
In Brief

In 2009, there were nearly 4.6 million drug-related emergency department (ED) visits of which about one half (49.8 percent, or 2.3 million) were attributed to adverse reactions to pharmaceuticals and almost one half (45.1 percent, or 2.1 million) were attributed to drug misuse or abuse.

In 2009, ED visits resulting from the misuse or abuse of pharmaceuticals occurred at a rate of 405.4 visits per 100,000 population compared with a rate of 317.1 per 100,000 population for illicit drugs.

ED visits involving misuse or abuse of pharmaceuticals increased 98.4 percent between 2004 and 2009, from 627,291 visits in 2004 to 1,244,679 visits in 2009.

ED visits involving adverse reactions to pharmaceuticals taken as prescribed increased 82.9 percent between 2005 and 2009, from 1,250,377 visits in 2005 to 2,287,273 visits in 2009.
Opioid and All Drug Overdose in the United States

Opioid pain relievers:

- Between 1999 and 2013, the number of opioid prescriptions increased 3-fold, from 76 million to 207 million.a
- Of the 22,767 deaths relating to pharmaceutical overdose in 2013, 71.3% involved opioid pain relieversa
- However, between 2011 and 2012, mortality due to opioid pain relievers declined 5%, the first such decrease in more than a decade.b,c

All Drugs:

- Drug overdose was the leading cause of injury death in 2012, causing more deaths in people aged 25 to 64 y than motor vehicle crashes.a

B  Deaths from Unintentional Drug Overdoses in the United States According to Major Type of Drug, 1999–2007

Pharmazeutische Gesellschaft Zürich / ETH
30. Januar 2014
National Overdose Deaths
Number of Deaths from Prescription Drugs

Source: National Center for Health Statistics, CDC Wonder
National Overdose Deaths
Number of Deaths from Rx Opioid Pain Relievers

Source: National Center for Health Statistics, CDC Wonder
National Overdose Deaths
Number of Deaths from Benzodiazepines

Source: National Center for Health Statistics, CDC Wonder
National Overdose Deaths
Number of Deaths from Cocaine

Source: National Center for Health Statistics, CDC Wonder
Zusammenfassung der US-Verhältnisse hinsichtlich tödlicher Überdosierungen

• Insgesamt lässt sich im Zeitraum 2001 bis 2013 erkennen, dass es bei allen medizinisch verordneten Suchttmitteln als auch bei Heroin und Kokain zu einer Zunahme der Todesfälle nach Überdosierung gekommen war. Die stärkste Zunahme liess sich für Heroin erfassen (5-fache Steigerung), gefolgt von Benzodiazepinen (4-fache Steigerung) und opioidhältigen Schmerzmitteln (3-fache Zunahme). Demgegenüber fiel der Zuwachs an Kokain-Toten mit 29 % geringradig aus.
Problemdroge Methadon

The Methadone Boom

Increasingly used as a painkiller, methadone is being prescribed in more regions of the country and deaths from its misuse are climbing.

Distribution of methadone per 100,000 people by three-digit ZIP code regions
Legitimate distribution to hospitals, pharmacies, practitioners and teaching institutions.

- 2001
- 2006

Data not available for areas in white.

Methadone-related poisoning deaths
Figures reported by each state from death certificates, which federal officials say may represent undercounting. Includes instances in which multiple drugs may have been present.

DEATHS PER 100,000 PEOPLE IN 2005

- 5

AGE OF THOSE WHO DIED IN 2005

- 14% Less than 24 years
- 22% 25-34 years
- 27% 35-44 years
- 29% 45-54 years
- 5% 55 years and older

Pct. of narcotic-related poisoning deaths (in which drug was named causal factor)

- Methadone
- Heroin
- Cocaine
- Other opiates*

*Includes morphine, codeine and hydrocodone

Sources: Centers for Disease Control and Prevention’s National Center for Health Statistics; Justice Department’s Drug Enforcement Administration
Vital Signs: Risk for Overdose from Methadone Used for Pain Relief — United States, 1999–2010

<table>
<thead>
<tr>
<th>Opioid</th>
<th>No.</th>
<th>Death rate per 100 kg MME</th>
<th>RR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All deaths</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>20</td>
<td>0.8</td>
<td>0.02</td>
<td>(0.01–0.04)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>364</td>
<td>7.7</td>
<td>0.28</td>
<td>(0.25–0.32)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>550</td>
<td>14.3</td>
<td>0.42</td>
<td>(0.38–0.47)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>74</td>
<td>9.1</td>
<td>0.27</td>
<td>(0.21–0.34)</td>
</tr>
<tr>
<td>Morphine</td>
<td>824</td>
<td>20.2</td>
<td>0.64</td>
<td>(0.58–0.70)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1,097</td>
<td>8.7</td>
<td>0.26</td>
<td>(0.24–0.28)</td>
</tr>
<tr>
<td>Methadone</td>
<td>1,034</td>
<td>33.6</td>
<td>1.00</td>
<td>referent</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3,294</td>
<td><strong>10.4</strong></td>
<td></td>
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</table>

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-drug deaths</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>2</td>
<td>0.1</td>
<td>0.01</td>
<td>(0.00–0.03)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>99</td>
<td>2.1</td>
<td>0.26</td>
<td>(0.21–0.33)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>42</td>
<td>1.1</td>
<td>0.11</td>
<td>(0.08–0.16)</td>
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<tr>
<td>Hydromorphone</td>
<td>4</td>
<td>0.5</td>
<td>0.05</td>
<td>(0.02–0.14)</td>
</tr>
<tr>
<td>Morphine</td>
<td>153</td>
<td>3.8</td>
<td>0.41</td>
<td>(0.34–0.50)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>150</td>
<td>1.2</td>
<td>0.12</td>
<td>(0.10–0.15)</td>
</tr>
<tr>
<td>Methadone</td>
<td>298</td>
<td>9.7</td>
<td>1.00</td>
<td>referent</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>748</td>
<td><strong>2.4</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** MME = morphine milligram equivalent; RR = rate ratio; CI = confidence interval.

* Counts for each opioid might not sum to the total shown for all deaths because some deaths involved more than one opioid.
Prescription Drug Addiction: Methadone Is The No. 1 Killer

The heroin-like painkiller methadone is the fastest-growing cause of narcotic deaths, according to federal government statistics, and ranks high among drugs implicated in the soaring rates of prescription drug addiction across the country.
Der Gebrauch von Arzneimitteln vs. verbotenen Substanzen unter Jugendlichen

**PRESCRIPTION/OVER-THE-COUNTER VS. ILLICIT DRUGS**

- Adderall: 7.4%
- Vicodin: 5.3%
- Cold Medicines: 5.0%
- Tranquilizers: 4.6%
- OxyContin: 3.6%
- Ritalin: 2.3%
- Marijuana: 36.4%
- K2/Spice: 7.9%
- MDMA/Ecstasy: 4.0%
- Salvia: 3.4%
- Powder Cocaine: 2.6%

*The percentage of 12th graders who have used these drugs in the past year.*
Another Reminder of the Terrible Toll of Addiction

This past weekend Americans were shocked and saddened to learn that one of our greatest actors, Philip Seymour Hoffman, had died at age 46 of an apparent heroin overdose. Hoffman’s death, in the prime of his life and career, is a poignant reminder of some of the harsh realities of a disease that 17.7 million Americans struggle with and that all too often cuts their lives short.
Kapitel 3: „Awareness raising“ in Europa

Dr. Mark L. Kraus
Dr. Mark L. Kraus


- Weiters fungierte er auch als co-Chairman des Buprenorphine Action Committees der ASAM, das dafür eintrat, dass die Anzahl der Patienten, die von einem Arzt mit Buprenorphin behandelt werden, von 30 auf 100 erhöht wurde.
Kraus war weiter der co-Chair in Fortbildungsveranstaltungen der US-Regierung (White House ONDCP Educational Summits). Er unterrichtete und führte Workshops über Suchtmedizin in etlichen Ländern durch, darunter auch in Rom, wo er das Panel im Rahmen der Global Addiction Conference leitete, das von der Litauischen Präsidentschaft erwähnt wurde. In Rom hielt er einen Vortrag vor Mitgliedern des Suchtkomitees des Europaparlaments und in Wilna sprach er vor den Drug Czars der Europäischen Union über die “Prescription Pain Pill Crisis in the USA and the world”..
DPA-NIDA Collaboration
& Research Networks

Workshop (Programma preliminare)

Roma, 25 luglio 2011

Sala Verde – Palazzo Chigi
Piazza Colonna 370 – Roma
Kapitel 4: Missbrauchssicherheit – Abuse deterrence
Excipient properties affecting the mechanical performance of abuse deterrent formulations

Development and Regulation of Abuse-Deterrent Opioid Medications – Public Meeting
October 30, 2014
Sheraton, Silver Spring, MD

Heather Boyce & Stephen W. Hoag, Ph.D.
NIPTE & UMB-School of Pharmacy
20 N. Pine St.; Baltimore MD 21201
Email: shoag@rx.umaryland.edu
Public Meeting on Abuse Deterrent Formulations: Framing the Meeting

Douglas C. Throckmorton, MD
Deputy Director for Regulatory Programs, CDER, FDA

October 30 & 31, 2014
Manufacturing Science of Abuse Deterrent Formulations (ADF): Testing and Standards

Mansoor A. Khan, Ph.D.

Director
Division of Product Quality and Research
OTR/OPS/CDER/FDA

Development and Regulation of Abuse-Deterrent Opioid Medications
Public Meeting

October 30, 2014
Abuse deterrent technologies

- FDA Draft Guidance for Industry: Abuse Deterrent Opioids- Evaluation and Labeling\(^1\) has identified 6 approaches to abuse deterrence
  - Physical/Chemical barrier
  - Agonist/Antagonist combinations
  - Aversion
  - Delivery System
  - Pro-drug
  - Combinations

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\(^1\) FDA Draft Guidance for Industry: Abuse Deterrent Opioids- Evaluation and Labeling (January 2013)
Zubereitungsstrategien

• Derzeit werden 4 Zubereitungsstrategien angewandt, um das Missbrauchspotential (abuse and misuse) psychoaktiver Arzneimittel abzuschwächen oder zu eliminieren. Diese sind:

• Typ 1 – Zubereitungen, die physisch die Möglichkeit beschränken, dass die Produkte mechanisch oder chemisch verändert werden können, um sie zu injizieren, sie zu inhalieren oder beschleunigt oral zu absorbieren. konsumieren.

• Typ 2 – Zubereitungen, die einen Antagonisten oder eine aversiv wirkende Substanz beinhalten, die beim Missbrauch die erwünschten Effekte blockieren oder sie widerwärtig oder toxisch machen, wenn sie für injizierenden der inhalierenden Gebrauch umgestaltet werden

• Typ 3 – Zubereitungen, bei denen die Freisetzung der Substanz modifiziert wird, um die rasche Absorption des aktiven Moleküls zu behindern. Das kann durch Pro-Drugs erreicht werden (molekulare Modifikation) oder durch eine Gestaltung des verzögerten Ausschüttung, die nur schwer durch mechanische, physische bzw. Küchenlabor – Prozeduren ausser Kraft gesetzt werden kann.

• Typ 4 - Die vierte Vorgangsweise kombiniert zwei oder mehr dieser Prozeduren. Meist wird dabei die Kombination zwischen modifizierter Freisetzung und physikalischer/chemischer Widerstandsfähigkeit angestrebt.
3 generelle Kategorien “missbrauchssicherer” Opioidzubereitungen

- Der “fortress approach,” bei dem die Zubereitung verzögert ausschüttet, auch wenn versucht wird, die Tablette zu zerteilen oder auzulösen z.B. Oxycontin ab 2010.

- Der “neutralisierende” Zugang, bei dem die Zubereitung zwar relativ leicht zu verändern ist, aber die Veränderung dazu führt, dass ein neutralisierender Antagonist ausgeschüttet wird, z. B. Suboxone und Embeda.

- Der “aversive” Zugang, in dem das Opioid an einen aversiven Zusatz gekoppelt ist, der zu unangenehmen Nebeneffekten führt, wenn eine größere Menge des Opioids eingenommen wird oder die Substanz verordnungswidrig gebraucht wird. Auf dem internationalen Markt befinden sich: Suboxone (buprenorphine), Embeda (morphine) und OxyContin (oxycodone). Es werden aber andere Substanzen entwickelt und von der FDA bewertet; z. B. Acurox, ein Kombo mit Niacin, das allerdings verworfen wurde.
Knowledge From ADF Submissions

DESIGN VARIATIONS

Type 1
Physical Barrier

Type 2
Aversion

Type 3
Agonist/Antagonist

Type 4
Complex delivery systems

Type 5 - Others
Others

SUBMITTED APPLICATIONS (IND, NDA, ANDA)

Multi-beads
Aversive Strategien

- Prinzipiell können die verschiedensten aversiv wirkenden Agentien zum Einsatz gebracht werden. Aufgelistet werden (Najib Babul, 2007):
  - Laxantien;
  - Substanzen, die die Hautgefäße erweitern
  - Substanzen, die Kopfschmerzen verursachen
  - Brechmittel und Brechreiz und Übelkeit erzeugende Substanzen
  - Bitterstoffe
  - Irritantien (Schleimhaut, Nasenschleimhaut, Mundschleimhaut, Bronchialschleimhaut), und Irritantien, die im Gastrointestinalsystem wirksam werden
  - Farbstoffe, die beschmutzend wirken
  - Stoffe, die Ausscheidungsprodukte entfärben;
  - übelriechende Zusätze;
  - Opioidantagonisten;
  - Benzodiazepinantagonisten (z. B., flumazenil), und Mischungen aller beschriebenen Agentien.
• The formulation optionally comprises auxiliary materials. Examples of these auxiliary materials (or pharmaceutically acceptable excipients) are (i) Binders such as acacia, alginic acid and salts thereof, cellulose derivatives, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, magnesium aluminum silicate, polyethylene glycol, gums, polysaccharide acids, bentonites, hydroxypropyl methylcellulose, gelatin, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, crospovidone, povidone, polymethacrylates, hydroxypropylmethylcellulose, hydroxypropylcellulose, starch, pregelatinized starch, ethylcellulose, tragacanth, dextrin, microcrystalline cellulose, sucrose, or glucose, and the like; (ii) Disintegrants such as starches, pregelatinized corn starch, pregelatinized starch, celluloses, cross-linked carboxymethylcellulose, crospovidone, cross-linked polyvinylpyrrolidone, a calcium or a sodium alginate complex, clays, alginates, gums, or sodium starch glycolate, and any disintegration agents used in tablet preparations;
• Issue: November/December 2014, Posted Date: 11/18/2014

• ABUSE-DETERRENT MARKET - What’s in the Pipeline? Abuse-Deterrent Products
<table>
<thead>
<tr>
<th>Type</th>
<th>Total</th>
<th>Approved / Marketed</th>
<th>Registration / Tentative Approval</th>
<th>Phase III</th>
<th>Phase II</th>
<th>Phase I or Bioequivalence</th>
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<tbody>
<tr>
<td>New Combination</td>
<td>3</td>
<td>2</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>New Formulation</td>
<td>25</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>1</td>
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<td>New Molecular Entity</td>
<td>5</td>
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<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
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<tr>
<td>OTC</td>
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<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic</td>
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<td>All</td>
<td>53</td>
<td>7</td>
<td>21</td>
<td>5</td>
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Active Pipeline & Approved Products by Type & Stage (All)
<table>
<thead>
<tr>
<th>Type</th>
<th>Total</th>
<th>Approved / Marketed</th>
<th>Phase I-III</th>
</tr>
</thead>
<tbody>
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<td>Type 1</td>
<td>9</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Type 2</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Type 3</td>
<td>19</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Type 4 (All)</td>
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<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Type 4a</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Type 4b</td>
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<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Type 4c</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Type 4d</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>33</td>
<td>5</td>
<td>28</td>
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</table>

Clinical Stage & Approved Products by Abuse-Deterrent Strategy
<table>
<thead>
<tr>
<th>Product</th>
<th>Active(s)</th>
<th>Company</th>
<th>Indication</th>
<th>Abuse Reduction Strategy</th>
<th>Approved</th>
<th>Dosage Form</th>
<th>First Approval</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vyvanse</td>
<td>Lisdexamfetamine</td>
<td>Shire</td>
<td>ADHD</td>
<td>Prodrug, ER</td>
<td>Global</td>
<td>Oral, Capsule</td>
<td>2007 (US)</td>
<td>Marketed</td>
</tr>
<tr>
<td>Embeda</td>
<td>Morphine, Naltrexone</td>
<td>Pfizer</td>
<td>Pain</td>
<td>Antagonist, ER</td>
<td>US</td>
<td>Oral</td>
<td>2009 (US)</td>
<td>Off Market</td>
</tr>
<tr>
<td>Targin</td>
<td>Oxycodone, Naloxone</td>
<td>Purdue Pharma</td>
<td>Pain</td>
<td>Antagonist, ER</td>
<td>US, EU, Other</td>
<td>Oral, Tablet</td>
<td>2009 (EU)</td>
<td>Marketed</td>
</tr>
<tr>
<td>OxyContin (Abuse Resistant)</td>
<td>Oxycodone</td>
<td>Purdue Pharma</td>
<td>Pain</td>
<td>Physical, ER</td>
<td>US, Canada</td>
<td>Oral, Tablet</td>
<td>2010 (US)</td>
<td>Marketed</td>
</tr>
<tr>
<td>Opana ER (Crush Resistant)</td>
<td>Oxymorphine</td>
<td>Endo</td>
<td>Pain</td>
<td>Physical, ER</td>
<td>US</td>
<td>Oral Tablet</td>
<td>2011 (US)</td>
<td>Marketed</td>
</tr>
<tr>
<td>Oxecta</td>
<td>Oxycodone</td>
<td>Acura</td>
<td>Pain</td>
<td>Physical</td>
<td>US</td>
<td>Oral, Tablet</td>
<td>2011 (US)</td>
<td>Marketed</td>
</tr>
<tr>
<td>Nexafed</td>
<td>Pseudoephedrine</td>
<td>Acura</td>
<td>Allergies</td>
<td>Physical</td>
<td>US</td>
<td>Oral, Tablet</td>
<td>2012 (US)</td>
<td>OTC</td>
</tr>
</tbody>
</table>

Global - includes, US, EU, Japan, and various other markets

Approved Abuse-Deterrent/Resistant Formulations
<table>
<thead>
<tr>
<th>Trade name</th>
<th>Opioid</th>
<th>Mechanism</th>
<th>FDA status</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin</td>
<td>Oxycodone</td>
<td>Hard plastic polymer that renders the tablet difficult to crush or dissolve</td>
<td>Approved in 2010</td>
</tr>
<tr>
<td>Remoxy</td>
<td>Oxycodone</td>
<td>Very viscous liquid intended to resist crushing, dissolution, injection, or inhalation</td>
<td>Under FDA review</td>
</tr>
<tr>
<td>Suboxone</td>
<td>Buprenorphine</td>
<td>Contains sequestered naloxone (an opioid antagonist), which is released when product is chewed/crushed and cancels the euphoric effects of buprenorphine</td>
<td>Approved in 2002</td>
</tr>
<tr>
<td>Embeda</td>
<td>Morphine</td>
<td>Contains sequestered naltrexone (an opioid antagonist), which is released when the product is chewed/crushed and cancels the euphoric effects of morphine</td>
<td>Approved in 2009</td>
</tr>
<tr>
<td>Acurox</td>
<td>Oxycodone (immediate release)</td>
<td>Contains an aversive agent (niacin) that causes unpleasant effects when injected, inhaled, or taken orally in high doses</td>
<td>Under FDA review</td>
</tr>
</tbody>
</table>

FDA indicates US Food and Drug Administration.
Der „Industry-Policy-Nexus“

Development and Evaluation of Abuse Deterrent Opioid Formulations, Part 1

FDA meeting on ADF
30 October 2014

Presented by Marta Sokolowska, PhD
On behalf of the Branded Industry Working Group
Excipient properties affecting the mechanical performance of abuse deterrent formulations

Development and Regulation of Abuse-Deterrent Opioid Medications – Public Meeting
October 30, 2014
Sheraton, Silver Spring, MD

Heather Boyce & Stephen W. Hoag, Ph.D.
NIPTF & UMB-School of Pharmacy
20 N. Pine St.; Baltimore MD 21201
Email: shoag@rx.umaryland.edu
Actions to Advance the Development and Adoption of Abuse-Deterrent Opioids

October 31st, 2014

Marina Brodsky, PhD, Pfizer, Inc.
On behalf of the Branded Industry Working Group

Alkermes, Collegium, Egalet, Endo, Grunenthal, INSYS, KemPharm, Mallinckrodt, Pain Therapeutics, Pfizer, Purdue, Reckitt Benckiser, Teva, Zogenix
Concluding Remarks

- Developing opioid analgesics with meaningful abuse-deterrent properties is an enormous challenge from a pharmaceutical perspective, to deliver on two opposing goals
  - Achieve the same release profile as the reference product without abuse-deterrent properties to ensure comparable analgesia when taken as directed
  - Prevent the release or counteract the effect of the opioid agent (i.e., display abuse-deterrent properties) only when the product is manipulated for abuse

- Individual companies would welcome an opportunity to participate in additional discussions regarding the complex scientific, regulatory, medical, and policy issues associated with abuse-deterrent opioids

- Given the crisis of opioid abuse, the time is now to advance the shared vision of a future in which most or all opioid analgesics are available to pain patients who need them in formulations that are less susceptible to abuse
Withdrawal of Currently Marketed Opioids Lacking Meaningful Abuse-Deterrent Properties

- Upon approval of new opioid analgesics with meaningful abuse-deterrent properties, the FDA should re-assess the risk-benefit of previously marketed non-abuse-deterrent versions*

- If the benefits of the non-abuse-deterrent opioid(s) no longer outweigh their risks, the FDA should require the sponsors, within 2-3 years, to withdraw for safety reasons both branded and generic versions of such products
  - The sponsors of such products can submit new data to support abuse-deterrent labeling

- The withdrawal should be contingent on
  - The new product with meaningful abuse-deterrent properties meeting the efficacy and safety needs of the pain patient, and maintaining its overall risk-benefit profile
  - The sponsor of the new product with meaningful abuse-deterrent properties working with the FDA and DEA to provide mitigation supply agreements against drug shortages

- Where the FDA has the authority to act they should take action; where they do not, the FDA should work with stakeholders to obtain the requisite authority

*Containing a particular opioid molecule with the same time release profile and duration (IR, ER 12hrs, ER 24hrs, etc.), route of administration (patch, oral), and indication (acute or chronic pain) as the previously marketed version
Refusal to Approve a New Opioid Lacking Meaningful Abuse-Deterrent Properties

- The FDA should not approve new opioids or opioid formulations that lack meaningful abuse-deterrent properties unless they fulfill an unmet need or provide a unique therapeutic benefit.

- FDA should encourage and support, through the development of guidance documents, a transition of all opioid products, both immediate and extended release, towards abuse-deterrent forms.

- Development of novel opioid analgesics or formulations that deter abuse via oral overconsumption is the focus of multiple ongoing efforts, however this goal has so far remained elusive.
Disclaimer

- The Branded Industry Working Group included representatives from the following 14 companies:
  - Alkermes
  - Collegium Pharmaceutical
  - Egalet Corporation
  - Endo Pharmaceutical Inc
  - Grunenthal
  - inSYS Therapeutics, Inc.
  - KemPharm, Inc.
  - Mallinckrodt Pharmaceuticals
  - Pain Therapeutics, Inc.
  - Pfizer, Inc.
  - Purdue Pharma L.P.
  - Reckitt Benckiser
  - Teva Pharmaceuticals Ltd.
  - Zogenix, Inc.

- The views expressed in this presentation represent the best available consensus of the Branded Industry Working Group as a whole
Development and Evaluation of Abuse Deterrent Formulations: A Generic Industry Perspective

October 30, 2014
Generics Industry Working Group

- Amneal Pharmaceuticals
- Kashiv Pharma
- Mallinckrodt Pharmaceuticals
- Osmotica Pharmaceuticals
- Par Pharmaceuticals

- Qualitest Pharmaceuticals
- Rhodes Pharmaceuticals
- Sandoz Pharmaceuticals
- Teva Pharmaceuticals
FDA: Stellungnahme in der Publikation des Meetings

• “Obwohl an die FDA die Aufforderung gerichtet wurde, von allen opioidhältigen Arzneimitteln, oder einigen speziellen Mitteln, zu for dern, dass sie mit Missbrauchs-abwehrenden Technologien zubereitet und produziert werden, sagten wir, dass eine derartige Forderung für die ganze Klasse dieser Arzneimittel derzeit weder möglich ist, noch auch im Interesse der öffentlichen Gesundheit. Das Gebiet ist noch in einem Frühstadium. Sowohl die angewandten technologien, wie auch die klinischen, epidemiologischen und statistischen Methoden um diese Technologien zu bewerten, sind neu und in rascher Entwicklung begriffen.”
Stop Tampering of Prescription Pills Act of 2013
113th Congress (2013-2014)

• H.R.486 -
• Committees: House - Energy and Commerce
• Latest Action: 02/08/2013 Referred to the Subcommittee on Health.
Kapitel 5: Biohazard
Der Povidon-Zwischenfall
• In einigen europäischen Ländern wurden Zubereitungen von Methadone, die als Zusatzstoff Povidon enthalten, zugelassen und vermarktet. Eine Lösung für den oralen Gebrauch wurde in Dänemark, Finnland, Malta, Norwegen, Schweden and im Vereinigten Königreich zugelassen; eine Tablettenform in Dänemark, Finnland, Ungarn, Island, Norwegen, Rumänien, Spanien und Schweden.
April 2014 wurde die Methadonlösung von Martindale Pharma in Norwegen von der Norwegian Medicinal Agency (NOMA) vom Markt genommen. July 2014 schloß sich die European Medicines Agency (EMA) dieser Entscheidung an, indem sie Martindale oral methadone Lösungen vom Markt nahm, die povidone (K90) enthielten. Grundlage der Entscheidung war die Überzeugung, dass in Skandinavien schwere und irreversible Organversagen bei Drogengebrauchern, die das orale Methadon für den Skandinavischen Markt, das Povidon K 90 enthielt, intravenös injiziert hatten, auf diese Zubereitung zurückzuführen war.

CMDh endorses suspension of methadone oral solutions containing high molecular weight povidone

The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)\(^1\) has endorsed by consensus the recommendation to suspend the marketing authorisation of methadone oral (by mouth) solutions containing high molecular weight povidone. These products will remain suspended until they have been reformulated. Additionally, the CMDh agreed that methadone tablets that contain low molecular weight povidone should remain on the market with changes to the product information.

Methadone is used in rehabilitation programs to prevent or reduce withdrawal symptoms in patients dependent on opioids such as heroin. Some oral formulations of methadone also contain the additive povidone, which is available in different molecular weights. While these medicines are intended for oral use only, some patients may misuse oral methadone formulations by injecting them into a vein. If a medicine containing high molecular weight povidone (known as K90) is misused in this way, the povidone is not excreted from the body and accumulates inside the cells of vital organs, which may cause serious harm.

The safety of oral methadone medicines containing povidone was reviewed by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC), following reports of serious adverse events in former or current drug abusers in Norway, which led to the suspension of methadone oral solutions containing povidone K90 from the Norwegian market.

The PRAC assessed the available safety data on the risks associated with the misuse by injection of methadone medicines containing povidone from post-marketing reports and the published literature, and a group of experts (which included pathologists and addiction experts) was consulted for advice. The PRAC concluded that risk minimisation measures would be insufficient to mitigate the risks with oral solutions containing high molecular weight povidone, and therefore recommended that these products should be suspended. They will need to be appropriately reformulated before being reintroduced on the European market.

For methadone tablets containing povidone of lower molecular weight (e.g. K25 and K30), the available data showed that this kind of povidone is excreted from the body and does not accumulate inside the cells as high molecular weight povidone does. Therefore, these products will remain on the

\(^1\) The CMDh is a medicines regulatory body representing the European Union (EU) Member States.
24 July 2014

- EMA/444346/2014 CMDh endorses suspension of methadone oral solutions containing high molecular weight povidone.
England, SUMMARY OF THE COMMISSION ON HUMAN MEDICINES MEETING HELD ON THURSDAY 19 JUNE 2014

• The Commission agreed with the MHRA and external experts that the UK should endorse the general recommendations of the PRAC assessments to suspend the marketing authorisation of methadone medicinal products for oral use containing high molecular weight povidone and that the condition for lifting the suspension should be reformulation of the product to remove povidone. The UK would not be affected by this suspension as there are no methadone products in clinical use in the UK that contain high molecular weight povidone.

• The Commission also endorsed the recommendation that consideration should be given to whether the potential safety issues this type of povidone highlighted by this review may also be applicable to other povidone-containing oral medicines that are known to or are likely to be injected by drug abusers.
Martindale, Wooburn Green, Buckinghamshire, 24th July 2014

• “Martindale Pharma, as a provider of life saving medicines is extremely disappointed at the CMDh decision to support the PRAC recommendation to suspend the Marketing Authorisation of methadone oral solutions containing high molecular weight povidone. This follows reports of pathological findings claimed to be linked to intravenous misuse of oral methadone in former or current drug abusers in Norway. Martindale Pharma’s methadone oral solution 2mg/ml, designed specifically to meet the needs of physicians and patients in Scandinavia – Norway, Sweden and Finland – is impacted by this decision”.
• The risk of harm is reduced with low molecular weight povidone since it is expected to be readily excreted and not to accumulate inside cells. Methadone tablets containing low molecular weight povidone remain on the market, but their product information will be amended to reinforce the recommendation that these medicines are for oral administration only and must not be used in any other way.
FDA-Regulierung: Liste der verbotenen Substanzen

- All intravenous drug products containing povidone.
- Povidone, marketed as Polyvinylpyrrolidone in Normal Saline, was found to be unsafe for use as a plasma expander in the emergency treatment of shock because povidone accumulates in the body and may cause storage disease with the formation of granulomas. Povidone also interferes with blood coagulation, hemostasis, and blood typing and cross matching. Approval of the NDA for Polyvinylpyrrolidone in Normal Saline was withdrawn on April 19, 1978 (see the Federal Register of April 7, 1978 (43 FR 14743)).
“The decision by CMDh is alarming as it puts patients at risk by jeopardising their access to an undoubtedly safe product they need when used as directed. Alternative methadone oral solution products have different pharmaceutical compositions and in the case of Finland there is no other licensed product available. Clearly the validity of the current EMA / PRAC process itself must be questioned. Our product is proven to be safe and effective when used correctly, as agreed by all parties throughout this process. There is no regulatory guideline which states that an oral solution has to be safe when misused which is the inference of the CMDh’s stated requirement for the suspension of Marketing Authorisation of our product to be lifted.”
• Martindale Pharma believe the process, as experienced by Martindale Pharma over the past weeks, has neither been fair nor reasonable and not in the long term interest of patients, public health or medical innovation.

• Martindale Pharma is a leading producer of safe, effective, regulated methadone products and, as part of medically supervised recovery programmes, its products are helping thousands of patients across Europe. The Company has always, and will continue, to work closely and in cooperation with Governments and health authorities to ensure that its opioid substitution products are used as intended and as a part of a comprehensive treatment system for opioid misuse.
• Martindale Pharma, headquartered in Wooburn Green, Buckinghamshire, UK, is a leading international specialty pharmaceutical company with sales in over 20 countries around the world. Its strategy is to build leading positions in five core business segments in areas of high unmet medical need, with strong growth potential and are opinion leader-led. These include Addiction, Critical Care and Wound Care. Martindale Pharma also has a leading position in the development and supply of Unlicensed Medicines.

• Martindale Pharma employs over 300 people, including a commercial team of over 50 people operating in the UK, Europe, Middle East, Australasia and Africa.
Martindale Pharma® launches three new products including first UK licensed Dexamfetamine Sulfate oral solution

Find out more

Martindale Pharma® launches Noyada®, the first ever licensed oral solution of captopril available in the UK

Find out more
Martindale: Physeptone (Methadon-Hydrochlorid) orale Lösung, 2,5 Liter-Flasche
Ben Frost
Kapitel 6: Bewertung
6.1. Positive Zeichen

• Ein geänderter Zugang zum Opioidabhängigen Individuum – es wird das Recht auf Behandlung postuliert

• Beschränkung der Gewinngier der Pharma-Industrie: z.B.: Ablehnung der Registrierung von „Acurox“ mit folgender Begründung:
The Acurox formulation of oxycodone, which added enough of the anti-cholesterol drug niacin to create uncomfortable sensations in those who swallowed too many pills, was likewise rejected, on grounds that the potential for curbing oxycodone abuse, deadly as it can be, still did not justify inflicting medically benign discomfort on abusers.
Draft Statement by the Scientific Network

To the Interactive discussion on high-level segment on substance demand reduction and related measures

1. Our statement is based on the recognition that the development, course and severity of substance use disorders are determined by the interface of developmental, biological, neuro-psychological, social, and cultural factors.

2. We encourage Members States to work toward the elimination of stigma and discrimination of individuals with substance use disorders. These are major roadblocks to effective interventions.

3. We consider that criminal sanctions are not beneficial to discourage their use.

4. We encourage Member States to collect and analyze substance use and substance related problems. This and prevention and treatment, and other types of interventions.

5. Substance use disorders are preventable, and effective in Member States to implement effective prevention and treatment, and to implement of effectiveness, in particular family-skills development and social skills building.

6. Substance use disorders are also treatable and should be seen as a public health issue rather than a criminal justice and/or moral issue. Individual should receive the state of the art treatment services, which are based on scientific evidence rather than ideology or beliefs. Our research clearly suggests that we can accomplish the best outcomes by combining and tailoring pharmacological and psycho-social interventions in the context of long term recovery management. However, it is important to emphasize that substance use disorders are chronic conditions with a tendency to reoccur. Effective treatment interventions are based on the chronic care strategies – the same we commonly use in treating patients with diabetes or hypertension.

7. Similar to any other medical condition, the treatment interventions should be consistent with the severity and chronicity of the substance use disorder. Thus for an emerging problem a brief intervention by a health practitioner might be sufficient whereas a more severe condition might require specialized care and long term treatment.

8. Treatment, rehabilitation, recovery management, and harm reduction are important elements of the continuum of care and should be considered, based on the unique needs of the individual.

9. Treatment of individuals with substance use disorders must be further integrated with the mainstream public health care delivery. Healthcare systems must engage in early identification and intervention for substance use disorders, and serve as linkage to other treatment settings.

10. The representatives of the scientific community are grateful to the United Nations, CND, UNODC, the Civil Society, and the Member States for reaching out to the scientific community. Our joint effort will help to bridge the gap between the science, the policy and practice.

11. We are willing to provide Member States with our expertise and support in preparation for the 2016 United Nations General Assembly Special Session on the World Drug problem.
6.2. Industrielle Problembereiche und neue Trends in den USA
Swing Is Alive

Swing in the right direction with 012h OxyContin II (Oxycodone HCI Controlled-Release) Tablets
Pacific Standard summarizes a pending civil suit brought by the State of Kentucky against Purdue Pharma. The privately held drugmaker is alleged (among other bad things) to have concealed evidence of overprescription and abuse of its best-selling OxyContin opiate.
Poison Pill

· FEB 23, 2015

How the American opiate epidemic was started by one pharmaceutical company.

The state of Kentucky may finally get its deliverance. After more than seven years of battling the evasive legal tactics of Purdue Pharma, 2015 may be the year that Kentucky and its attorney general, Jack Conway, are able to move forward with a civil lawsuit alleging that the drugmaker misled doctors and patients about their blockbuster pain pill OxyContin, leading to a vicious addiction epidemic across large swaths of the state.

A pernicious distinction of the first decade of the 21st century was the rise in painkiller abuse, which ultimately led to a catastrophic increase in addicts, fatal overdoses, and blighted communities. But the story of the painkiller epidemic can really be reduced to the story of one powerful, highly addictive drug and its small but ruthlessly enterprising manufacturer.
Aber gleichzeitig
Ten years ago, prescription painkiller dependence swept rural America. As the government cracked down on doctors and drug companies, people went searching for a cheaper, more accessible high. Now, many areas are struggling with an unprecedented heroin crisis.
Unintentional Drug Poisoning Deaths Involving Opioid Analgesics, Cocaine and Heroin: United States, 1999–2011

% CHANGE 2006-11

Number of Deaths

16,000
14,000
12,000
10,000
8,000
6,000
4,000
2,000


- 35%
+ 119%
+ 28%
National Overdose Deaths
Number of Deaths from Heroin

Source: National Center for Health Statistics, CDC Wonder
2) Arzneimittel wie verschreibungspflichtige Opiode können nicht aus der rein medizinischen Perspektive als Schmerzmittel oder in anderen Indikationsbereichen angesehen werden. In diesem Kontext gibt es nicht nur Seiteneffekte für die betroffenen Patienten, sondern auch im Bereich der öffentlichen Gesundheit Seiteneffekte für die Gesellschaft; z. B. die Möglichkeit der Diversion und die daraus resultierende auf Überdosis beruhende Mortalität.

(zit. aus dem Abschlussbericht von ALICE RAPS)
Die Position des Arztes

• Der Arzt steht in der Umsetzung dieser gesellschaftspolitischen Forderung an letzter und exponierter Stelle. Er ist gezwungen, den Auftrag am einzelnen Patienten umzusetzen.
Ist es noch als medizinische Aufgabe zu betrachten, bzw. mit der ärztlichen Ethik in Einklang zu bringen, Arzneimittel zu verschreiben, die aufgrund ihrer Zubereitung toxischer sind als das notwendige und in der Zubereitung vorhandene und verordnete Mittel?

Ist es mit der ärztlichen Ethik in Einklang zu bringen, Arzneimittel abzugeben, die dem Konsumenten einen Schaden zufügen können?

Ist nicht auf jeden Fall der Patient als Partner in der Arzt-Patient – Beziehung zu informieren und in der Folge berechtigt, die Einnahme einer derartigen Zubereitung zu verweigern?
Kapitel 8: Zusammenfassung, Schlussfolgerungen, Ausblick

• Missbrauchssicherheit ist und bleibt ein großes Thema, das von großer wirtschaftlicher Bedeutung ist und dem sicherheitspolitische und gesundheitspolitische Bedeutung zugeordnet wird.

• Manche Repräsentanten der Pharmaindustrie scheinen recht rücksichtslos, was negative Auswirkungen auf die opioidabhängige Klientel betrifft; es bestehen aber Anzeichen dafür, dass sie von gesundheitspolitischer und Menschenrechtlicher Seite zum Überdenken ihrer Haltung gezwungen wird.
Neue Aufgabenstellungen

• Das Konzept der Missbrauchssicherheit ist nicht beschränkt auf die „klassische“ Substitutionsbehandlung. Es bezieht sich auf die Entwicklung von Arzneimitteln zur Substitution, zur Schmerztherapie, zur Behandlung affektiver Störungen, etc. Grundsätzlich könnten die neuen Technologien bei allen Medikamenten zum Einsatz gebracht werden.
ALKS-5461 is a new drug that is being developed by the company Alkermes as an alternative to SSRI’s for the treatment of depression. ALKS-5461 (its trial name) is a combination of both buprenorphine (suboxone) and samidorphan, and is regarded as a non-addictive opioid modulator and antidepressant. It is currently being developed specifically as an antidepressant augmentation strategy in cases of treatment-resistant depression.

This drug is also being developed with the intention of treating cocaine dependence, and Alkermes has received a grant from the National Institute on Drug Abuse (NIDA) for the drug’s development. Initial research suggests that the drug produces a powerful antidepressant response within a week of treatment, in nearly everyone that takes it. Additionally the side effect profile appears to be relatively minimal.
Alkermes Announces Positive Results of Phase 2 Clinical Trial of ALKS 3831 in Schizophrenia

• January 07, 2015

• — Once-Daily, Oral Product Candidate Showed Efficacy Equivalent to Olanzapine With Clinically Meaningful and Statistically Significant Lower Weight Gain in 300-Patient Study — ALKS 3831 is composed of samidorphan, a novel, potent mu-opioid antagonist, in combination with the established antipsychotic drug, olanzapine.

• — Company Plans to Initiate Pivotal Development Program in 2015 —
• In dieser Situation erwächst den Ärzten, die in diesen Berufsfeldern arbeiten, eine neue Aufgabe: sie müssen mehr als bisher auch auf die Zusatz- und Füllstoffe der Arzneimittelspezialitäten achten und über deren Risiken informiert sein, um ihre Patienten und Patientinnen ausreichend informieren zu können.
Opioid Abuse in the U.S. and HHS Actions to Address Opioid-Drug Related Overdoses and Deaths, März 2015

HHS (U.S. Department of Health and Human Services) and Secretary Burwell are focused on three priority areas to reach these goals and to combat opioid abuse:

• Opioid prescribing practices to reduce opioid use disorders and overdose
• The expanded use of naloxone, used to treat opioid overdoses
• Expanded use of Medication-assisted Treatment (MAT) to reduce opioid use disorders and overdose
Auswirkungen auf das Konzept der Risikominimierung
Spannung zwischen der Produktion von missbrauchssicheren Zubereitungen und der Bereitstellung von Materialien, die diese antagonisieren oder ihre Wirksamkeit einschränken.
Ich danke für Ihre Aufmerksamkeit
Gebrauch von Opioiden mit verzögerter Freisetzzung?
Giftspritze adé:

Europa sperrt Barbiturate weg

Die USA in der Isolation: Aus Protest gegen die Todesstrafe weigern sich immer mehr Länder, ein wichtiges Arzneimittel für die Giftspritze zu liefern. Jetzt reagiert auch die EU.
• Have you guys seen these commercials? As soon as I saw it I was like: LOOK! Suboxone Commercial!

• Although they NEVER say "Suboxone" or anything during the whole commercial. They just tell you to go to Turntohelp.com. Very discreet. Weird.

• Anyway, what do you guys think? I think it's great. Now if RB could just get on the physician education things might improve for addicts.

• ___________________
  • You can't stop the waves, but you can learn to surf.

• -Jack Kornfield
• Parenteral buprenorphine-naloxone abuse is a major cause of fatal buprenorphine-related poisoning.

• Häkkinen M, Heikman P, Ojanperä I.

• Author information

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• Abstract
Häkkinen M, Heikman P, Ojanperä I. Parenteral buprenorphine-naloxone abuse is a major cause of fatal buprenorphine-related poisoning.

- Buprenorphine (BPN) medication for opioid maintenance treatment in Finland consists predominantly of buprenorphine-naloxone (BNX). Both BPN and BNX are associated with diversion, abuse and non-medically supervised use worldwide. Our purpose was to estimate the proportion of BNX to all BPN-related fatalities. The material consisted of 225 deceased drug abusers in Finland from January 2010 to June 2011 with a positive BPN and/or norbuprenorphine (NOR) and/or naloxone (NX) finding in urine. The data were divided into three groups based on the urine NX and BPN concentrations. The "Parenteral BNX" group (>100 μg/l NX) was presumed to consist of injecting or snorting BNX abusers and the "Parenteral BPN" group (>50 μg/l BPN, 0 μg/l NX) of injecting or snorting BPN abusers, while the "Other BNX or BPN" group (≤100 μg/l NX, or ≤50 μg/l BPN combined with 0 μg/l NX) was presumed to consist of mainly sublingual BNX or BPN users. In 12.4% of cases the NX urine concentration was higher than the threshold 100 μg/l. In fatal BPN poisonings, the proportion of parenteral BNX was 28.4%. In the "Parenteral BNX", "Parenteral BPN" and "Other BNX or BPN" groups, the proportion of fatal BPN poisonings was 67.9, 31.0 and 22.6%, respectively. BNX abuse can be fatal. Among the 225 BPN-related fatalities, parenteral abuse of BNX was shown to be common (12.4%) and BNX poisoning was the underlying cause of death in 8.4%. Parenteral BNX caused fatal BPN poisoning proportionally more often than parenteral BPN.