



**Kinder- und Jugend-
psychiatrie / Psychotherapie**

Universitätsklinikum Ulm

Medikamentöse Behandlung von gehemmten und depressiven Jugendlichen – Verhaltensaktivierung als Gefahr?

Michael Kölch

**Tagung Amok
Ulm 2.12. 2009**





**Kinder- und Jugend-
psychiatrie / Psychotherapie**

Universitätsklinikum Ulm

Disclosure

Forschungsförderung:

BMBF

BMFFSJ

Schweizer Bundesamt für Justiz

Eli Lilly International Foundation

Boehringer Ingelheim

Europäische Akademie

Mitarbeit in klinischen Studien

Eli Lilly

Astra Zeneca

Janssen-Cilag

Reisebeihilfen/Vortragshonorare:

Janssen-Cilag

Universität Rostock

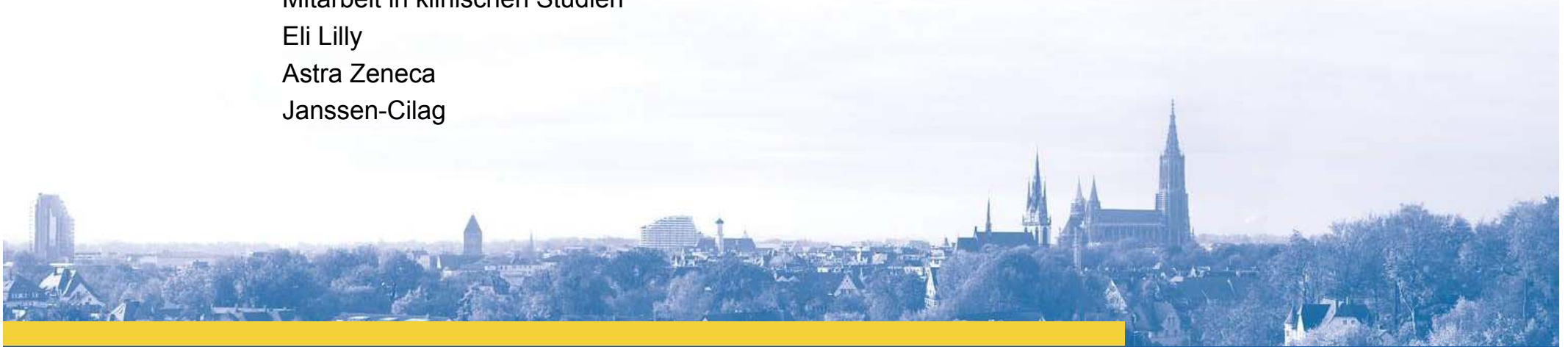
DGKJPP

UCB

diverse gemeinnützige

Organisationen

Keine Aktien, keine Beteiligungen an
Pharmafirmen





Warum Antidepressiva bei depressiven Störungen ? Entscheidungsrationale für eine medikamentöse Therapie



Depressive Störungen

- ▶ enorme Auswirkungen auf Lebensqualität der Betroffenen

Bei Kindern und Jugendlichen: Schulleistungen, peer-group, soziales Funktionsniveau

- ▶ immense Folgekosten

für das Gesundheitssystem,

wie auch die Volkswirtschaften insgesamt

(WHO 2002, Grünbuch der EU 2005)

Scheinbares Paradoxon:

- ▶ ungefähr 50 % der Erkrankungen zeigen einen bis in das Erwachsenenalter andauernden Verlauf (Weissman et al. 1999)

- ▶ andererseits remittiert fast die Hälfte der Depressionen bei Minderjährigen innerhalb eines Jahres (NICE 2005)



Suizidalität, Suizide und Depression

► Depression erhöht das Risiko für einen Suizid (Harrington 2001)

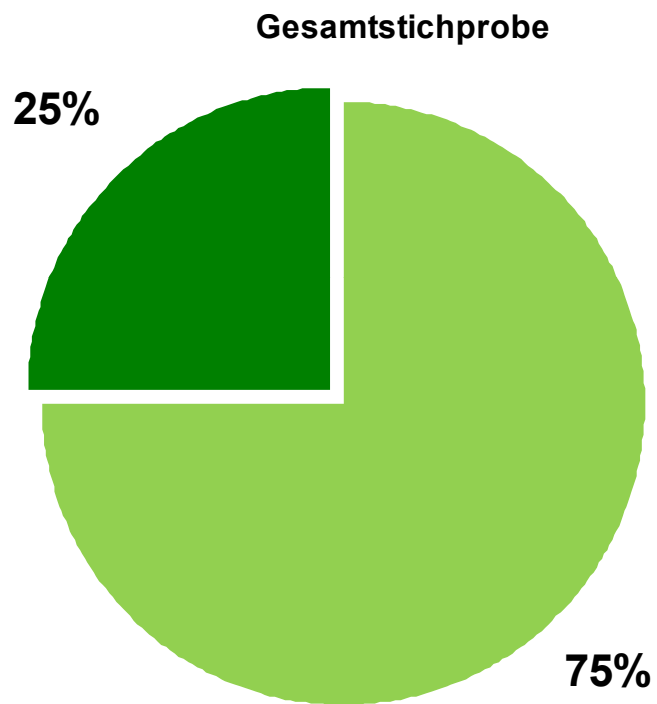
Risiko nicht nur während der Erkrankung, sondern auch in der Phase der Besserung erhöht! (Nelson et al., 2007)

Suizidale Gedanken und Suizidversuche sind bei depressiven Minderjährigen in Behandlung gehäuft im Vergleich zur Normalbevölkerung:

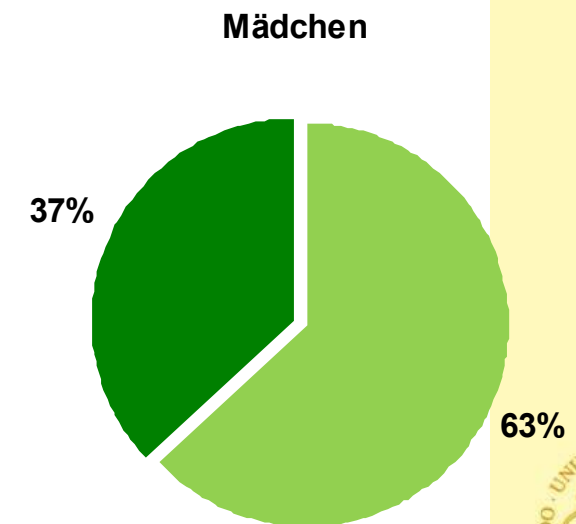
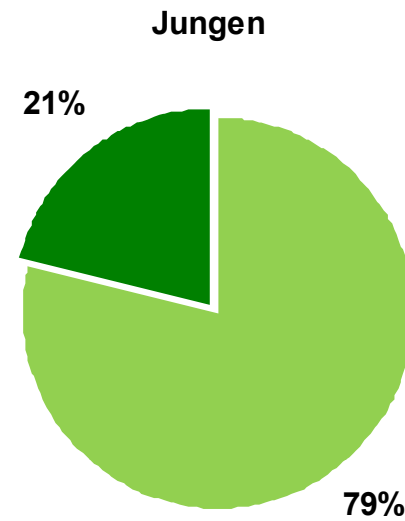
35-50% dieser Jugendlichen hatten oder unternehmen einen Suizidversuch. Zwischen 2-8% begehen Suizid innerhalb von 10 Jahren.



Internalisierende Störungen MAZ; Schweizer Heimkinder



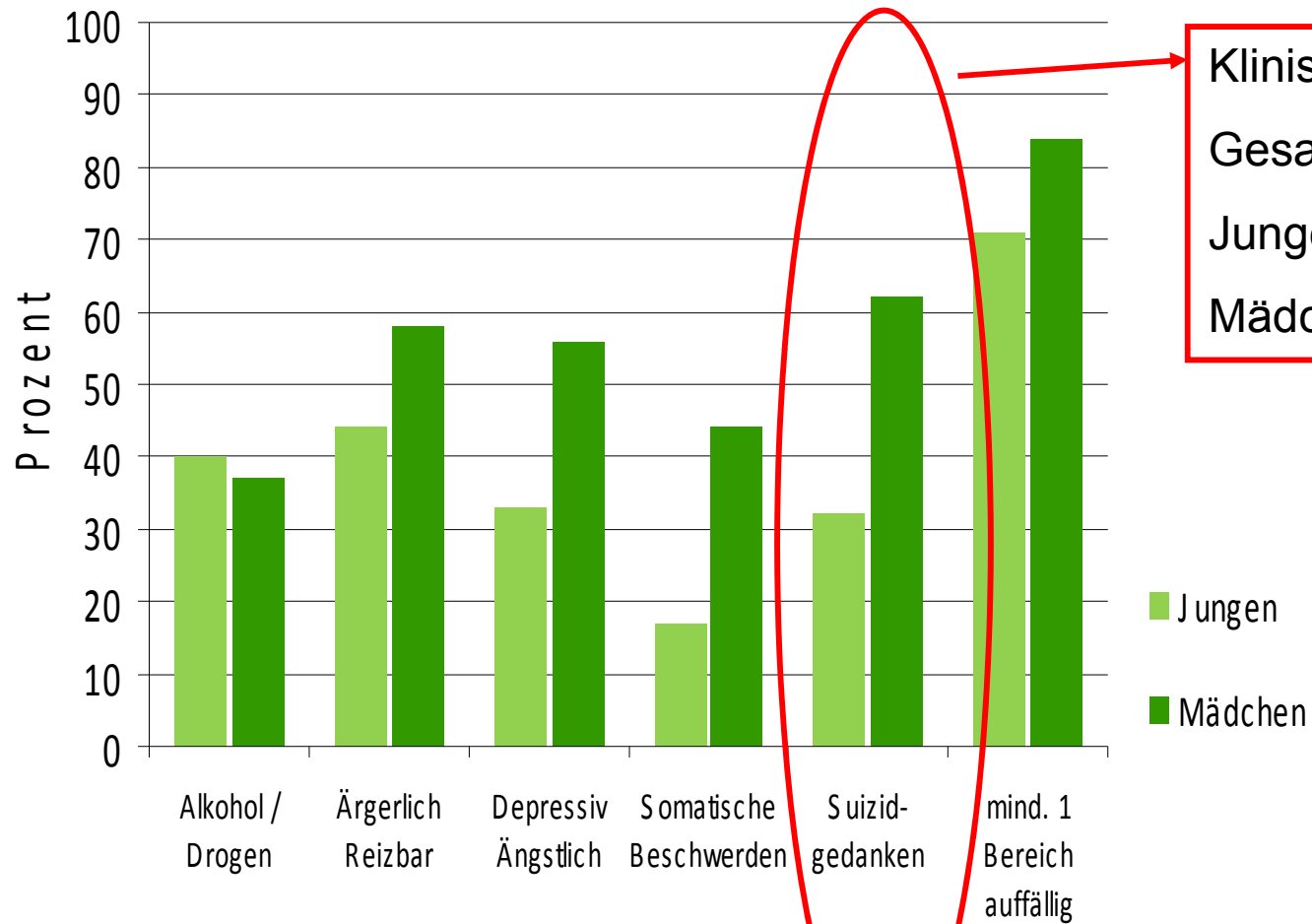
■ nein
■ ja



N=288 (m: 215; w: 73)



Maysi: Suizidgedanken



Klinisch auffällig:
Gesamtstichprobe: 40%
Jungen: 32%
Mädchen: 62%

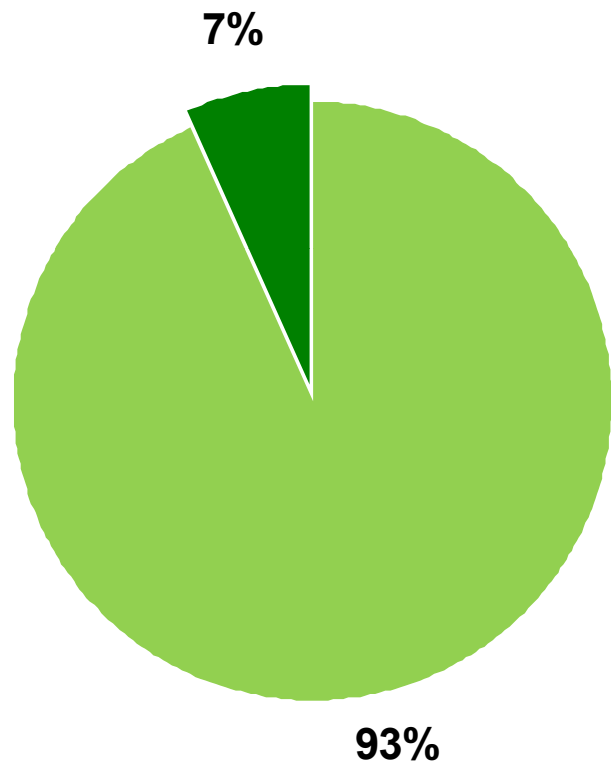
N=301 (m: 222; w: 79)





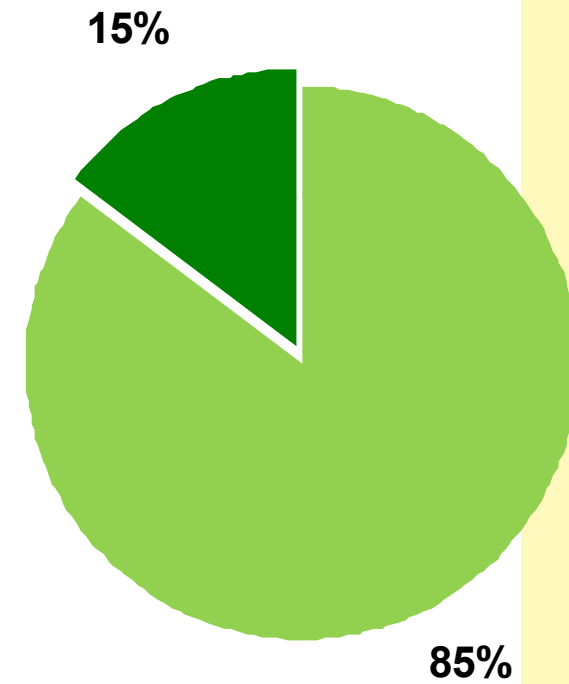
Depressive Störungen (F32, F33, F38, F39)

Jetzige Episode



Episode in der Vergangenheit

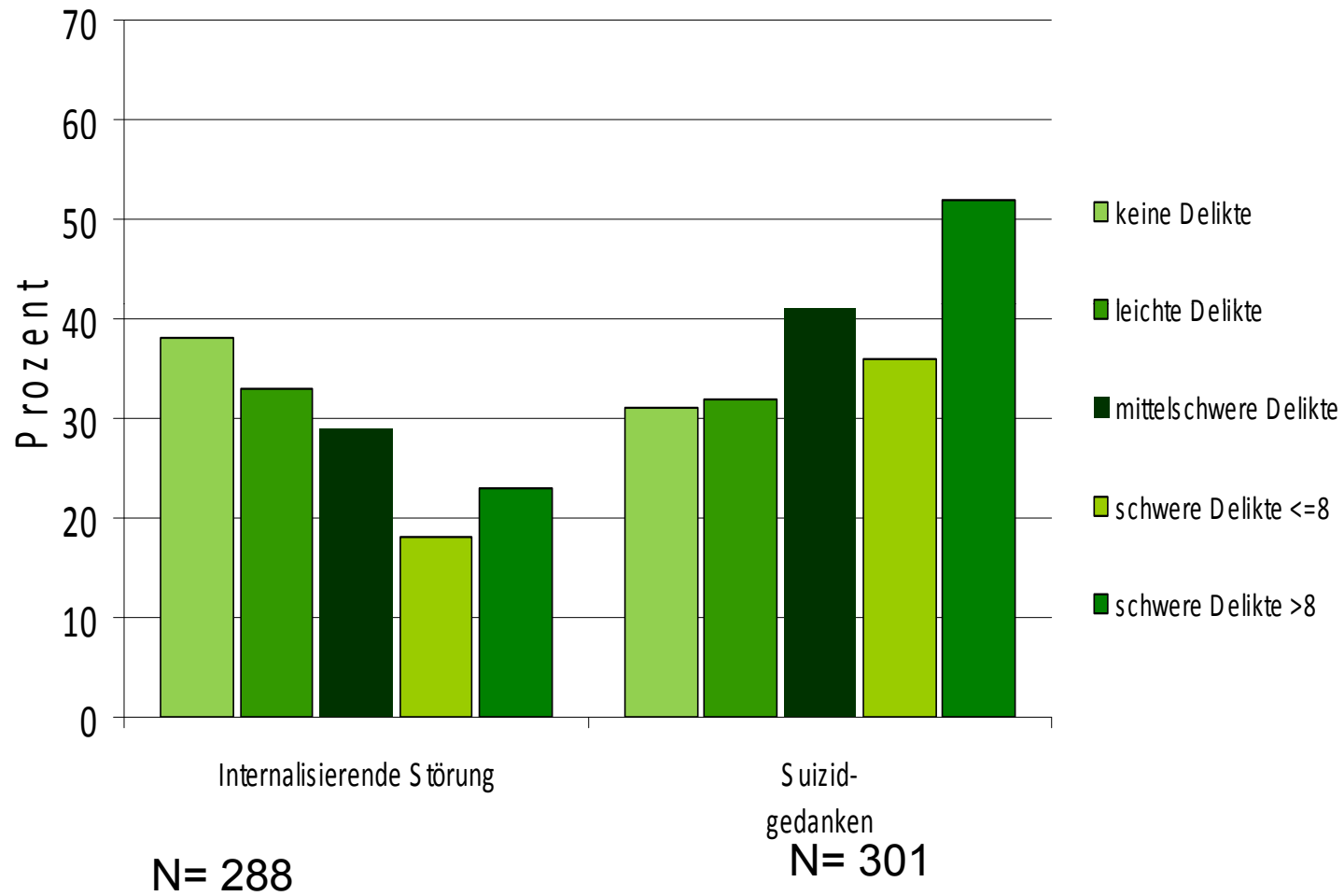
nein
ja



N=288



Deliktschwere





Medikamentöse Intervention: wann?

Alle Leitlinien machen Einsatz pharmakotherapeutischer Interventionen vom Schweregrad bzw. der psychosozialen Funktionsbeeinträchtigung abhängig

NICE:

Vorgeschaltet 3-6 Sitzungen Psychotherapie/psychosoziale Intervention - wenn keine (ausreichende) Besserung/Veränderung: Indikation für Pharmakotherapie

DGKJPP:

Nur als Teil eines therapeutischen Gesamtplans nach eingehender kinder- und jugendpsychiatrischer Diagnostik und Erhebung des somatischen Status

Besonders bei schweren Formen und bei Suizidalität zu erwägen

Texas Children's Medication Algorithm Project

The use of the recommended antidepressant medications requires ... consideration of other evidence-based treatment alternatives such as cognitive behavioral therapies.





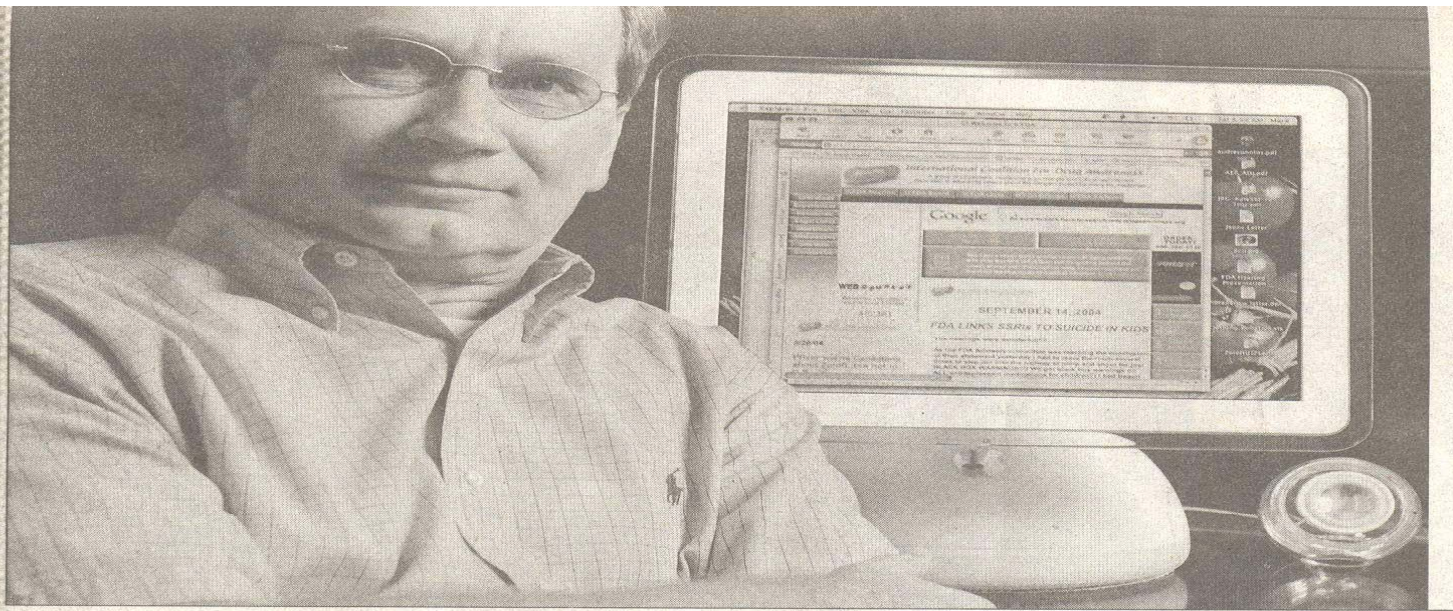
Aktuelle Fragen bei der Therapie der depressiven Erkrankungen bei Minderjährigen

Bestehen spezifische Nebenwirkungen bei Minderjährigen, die durch klinische Prüfungen bei Erwachsenen nicht erkannt werden? Neben bekannten physiologischen Besonderheiten bei MJ ICH-groups („Kinder sind keine kleinen Erwachsenen“) auch auf Verhaltensebene Besonderheiten ?

„Behavioural toxicity“

Damit ist eine vermehrte Aktivierung des Patienten gemeint, die einen Zusammenhang mit suizidalen Gedanken und Verhalten haben kann (Hammad 2004).

► „Black-box“-warnings durch FDA und EMEA/nationale Zulassungsbehörden



SEA CHANGE: Mark Miller's website highlights risks for children taking antidepressants. Miller was instrumental in getting the FDA to issue warnings on the drugs. In 1997, Miller's 13-year-old son, Matt, killed himself after he started taking an antidepressant. Photographs by L.G. Patterson For the Times

Parents' Crusade Forces Dangers of Antidepressants Into Spotlight

Too many found out too late about suicide and violent behavior risks in children and demanded a response from the government.

By ELIZABETH SHOGREN
Times Staff Writer

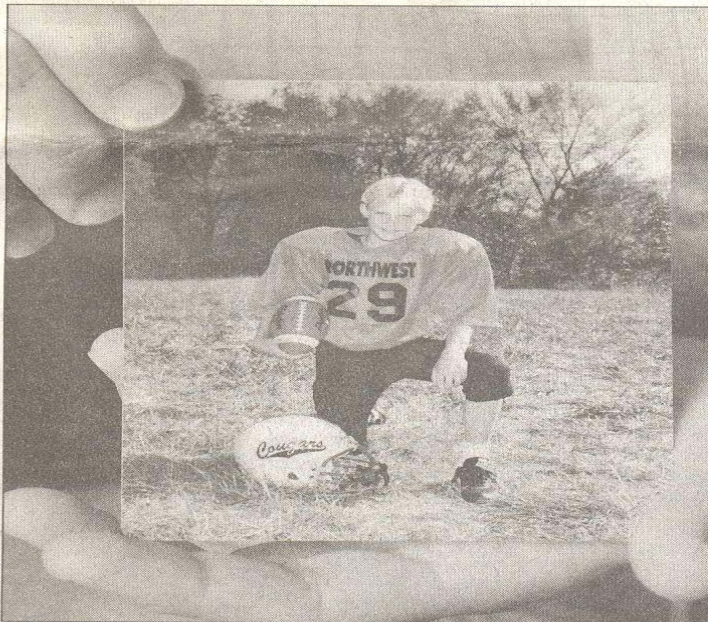
WASHINGTON — Seven years ago, Mark Miller's 13-year-old son, Matt, who loved to ride bikes and play video games and excelled at making origami animals, hanged himself in his bedroom closet. His parents were devastated — and mystified.

"He had never threatened suicide," Miller recalled. "The only thing that had changed that week in his life was the medication."

Seven days before his death, Matt had begun taking Zoloft, a popular antidepressant prescribed by his doctor.

His father, struggling to understand what had happened, dived into the Internet, where he found books on the risks of antidepressants. He was soon convinced that the drug had caused Matt's death.

Miller helped start a website about the risks of the anti-



LOST TO SUICIDE: Matt Miller at age 11. He hanged himself when he was 13 while taking Zoloft.

But while on the antidepressant, Michelle, who had never attempted to harm herself or others, slammed her brother's head into a wall, went after another teenager with a baseball bat and attempted to take her own life. Van Syckel came across Miller's drug awareness website in 2002, as she was trying to ease her daughter of Paxil. Soon she was spending most of her time trying to get someone in power to warn other parents of the dangers of antidepressants. Most political leaders ignored her letters; one exception was Sen. Charles E. Schumer (D-N.Y.), who asked her to join him at a news conference in New York calling on the FDA to discourage the use of Paxil by children.

Then she turned to her own congressman, Rep. Michael Ferguson (R-N.J.). Ferguson became a major force behind a House subcommittee's investigation of the safety of the antidepressants and the role of drug companies and the FDA. "It was [Van Syckel] who really got my attention and prompted me to take an active and leading role," Ferguson said. It was not easy, he said, to get members of Congress to focus on the issue during an election year, when the country was already absorbed by terrorism and the





Emotional Lability

Adverse event text was searched in the following way:

Preferred term is '*emotional lability*'

and the verbatim term includes any reference to:

'*attempt*'

'*cut*'

'*gas*'

'*hang*'

'*hung*'

'*jump*'

'*mutilat*' [includes '*mutilate*', '*mutilated*', '*mutilation*']

'*overdos*'

'*self damag*' or '*self-damag*'

'*self harm*' or '*self-harm*'

'*self inflict*' or '*self-inflict*'

'*self injur*' or '*self-injur*'

'*shoot*'

'*slash*'

'*suic*'

or the preferred term is '*overdose*' or '*intentional overdose*'.



Besonderheit „behavioural toxicity“ bei Minderjährigen

Altersspezifische Unterschiede bei Nebenwirkungen von SSRI (Safer & Zito 2006):

Erbrechen:	Kinder > Jugendliche
Aktivierung/„beh. toxicity“:	Kinder > Jugendliche > Erwachsene
Risiko für „Suizidalität“:	SSRI 4%, Placebo 2%
Relatives Risiko:	Suizidalität: 1,95 (95% KI 1,28-2,98) parasuizid. Handl.: 1,90 (1,00-3,63) Suizidgedanken: 1,74 (1,06-2,86)

(Hammad 2006 & Mosholder et al. 2006)

Dubicka et al. (2006): Metaanalyse Daten Committee on Safety of Medicines (CSM) + Literatursuche 2004-2005

Self-harm/suicide related behaviour bei knapp 5% (71) Jugendlichen vs. 3% (38) Pbo

Suizidale Gedanken/suizidale Impulse nicht statist. signifikant häufiger

NNT für SSRI bei MDD: 10 (7-15); NNH 143 (Bridge 2007)





Für andere Therapieverfahren: Nebenwirkungen nicht immer gut belegt!

Suicide Attempts Among Patients Starting Depression Treatment With Medications or Psychotherapy

Gregory E. Simon, M.D., M.P.H.

James Savarino, Ph.D.

Objective: This study compared the time patterns of suicide attempts among outpatients starting depression treatment with medication or psychotherapy.

Method: Outpatient claims from a pre-paid health plan were used to identify new episodes of depression treatment beginning with an antidepressant prescription in primary care (N=70,368), an antidepressant prescription from a psychiatrist (N=7,297), or an initial psychotherapy visit (N=54,123). Outpatient and inpatient claims were used to identify suicide attempts or possible suicide attempts during the 90 days before and 180 days after the start of treatment.

Results: Overall incidence of suicide attempt was highest among patients receiving antidepressant prescriptions from psychiatrists (1,124 per 100,000), lower among those starting psychotherapy (778 per 100,000), and lowest among those re-

ceiving antidepressant prescriptions in primary care (301 per 100,000). The pattern of attempts over time was the same in all three groups: highest in the month before starting treatment, next highest in the month after starting treatment, and declining thereafter. Results were unchanged after eliminating patients receiving overlapping treatment with medication and psychotherapy. Overall incidence of suicide attempt was higher in adolescents and young adults, but the time pattern was the same across all three treatments.

Conclusions: The pattern of suicide attempts before and after starting antidepressant treatment is not specific to medication. Differences between treatments and changes over time probably reflect referral patterns and the expected improvement in suicidal ideation after the start of treatment.

(Am J Psychiatry 2007; 164:1029–1034)



Depressive Symptoms and Clinical Status During the Treatment of Adolescent Suicide Attempters Study

BENEDETTO VITIELLO, M.D., DAVID BRENT, M.D., LAURENCE L. GREENHILL, M.D.,
GRAHAM EMSLIE, M.D., KAREN WELLS, PH.D., JOHN T. WALKUP, M.D.,
BARBARA STANLEY, PH.D., OSCAR BUKSTEIN, M.D., BETSY D. KENNARD, PSY.D.,
SCOTT COMPTON, PH.D., BARBARA COFFEY, M.D., MARY F. CWIK, PH.D.,
KELLY POSNER, PH.D., ANN WAGNER, PH.D., JOHN S. MARCH, M.D., MARK RIDDLE, M.D.,
TINA GOLDSTEIN, PH.D., JOHN CURRY, PH.D., LISA CAPASSO, B.A., TARYN MAYES, M.S.,
SA SHEN, PH.D., SONIA S. GUGGA, M.S., BLAKE J. TURNER, PH.D., SHANNON BARNETT, M.D.,
AND JAMIE ZELAZNY, B.S.N., M.P.H.

ABSTRACT

Objective: To examine the course of depression during the treatment of adolescents with depression who had recently attempted suicide. **Method:** Adolescents ($N = 124$), ages 12 to 18 years, with a 90-day history of suicide attempt, a current diagnosis of depressive disorder (96.0% had major depressive disorder), and a Children's Depression Rating Scale-Revised (CDRS-R) score of 36 or higher, entered a 6-month treatment with antidepressant medication, cognitive-behavioral therapy focused on suicide prevention, or their combination (Comb), at five academic sites. Treatment assignment could be either random or chosen by study participants. Intent-to-treat, mixed effects regression models of depression and other relevant ratings were estimated. Improvement and remission rates were computed with the last observation carried forward. **Results:** Most patients ($n = 104$ or 84%) chose treatment assignment, and overall, three fourths ($n = 93$) received Comb. In Comb, CDRS-R declined from a baseline adjusted mean of 49.6 (SD 12.3) to 38.3 (8.0) at week 12 and to 27.0 (10.1) at week 24 ($p < .0001$), with a Clinical Global Impression—defined improvement rate of 58.0% at week 12 and 72.2% at week 24 and a remission (CDRS-R ≤ 28) rate of 32.5% at week 12 and 50.0% at week 24. The CDRS-R and the Scale for Suicidal Ideation scores were correlated at baseline ($r = 0.43$, $p < .0001$) and declined in parallel. **Conclusions:** When vigorously treated with a combination of medication and psychotherapy, adolescents with depression who have recently attempted suicide show rates of improvement and remission of depression that seem comparable to those observed in nonsuicidal adolescents with depression. *J. Am. Acad. Child Adolesc. Psychiatry*, 2009;48(10):00–00. **Key Words:** adolescents, suicide, depression, treatment. Clinical trial registration information—Treatment of Adolescent Suicide Attempters (TASA). URL: <http://clinicaltrials.gov>. Unique identifier: NCT00080158.





Nach 2004 dramatischer Rückgang der Verordnungen in USA und einigen europäischen Ländern

Nemeroff et al. 2007

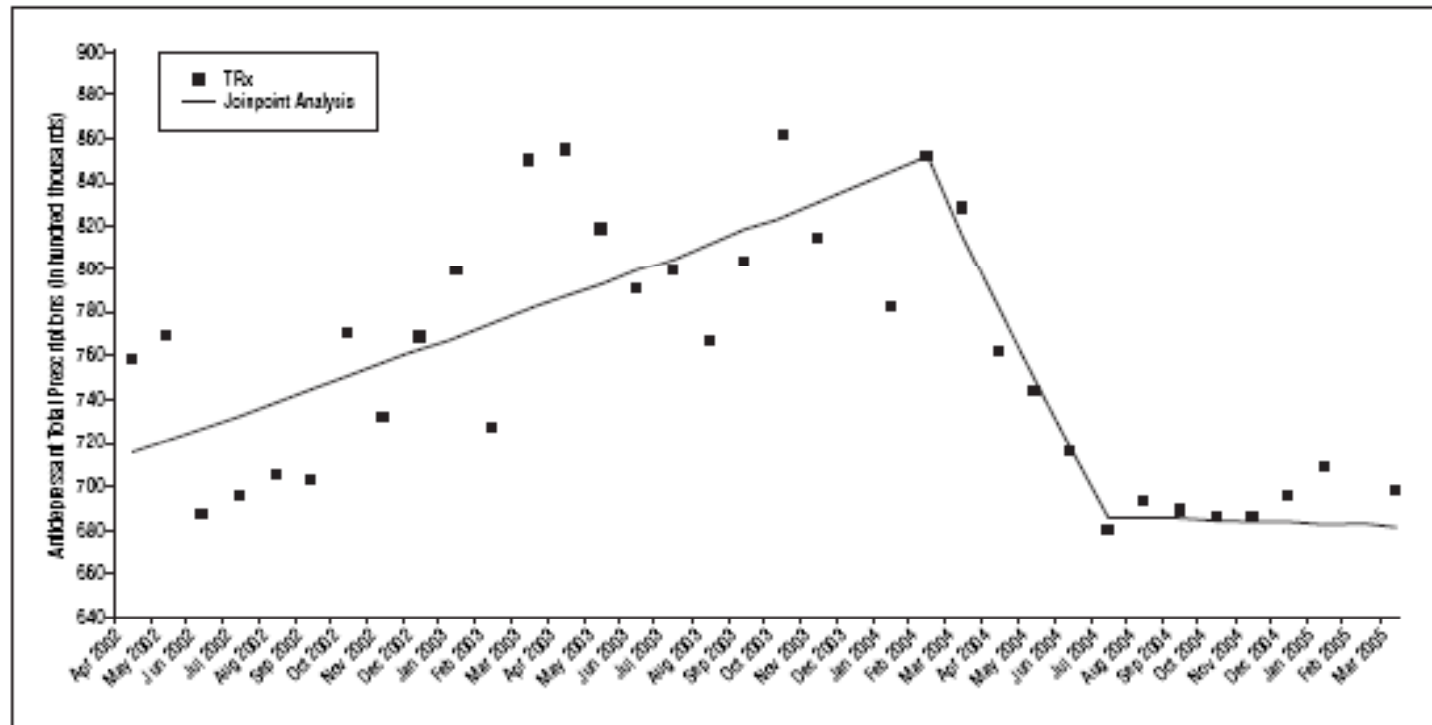


Figure 3. Antidepressant prescribing trend among those from birth to the age of 17 years.⁶⁴ In October 2003 and March 2004, there were Food and Drug Administration (FDA) public health advisories; and in September 2004, there was an FDA advisory panel meeting. TRx indicates total prescriptions. *Arch Gen Psychiatry.* 2007;64:466-472

- Rückgang der Verschreibungsquoten von SSRI bis zu 25%
- Zusammenhang mit ansteigenden Suizidraten? Gibbons et al. 2006



Veränderungen im Verordnungsverhalten

72% (n = 484) of respondents were aware of the FDA warning. Of the 484 respondents who were aware of the warning, 80% (n = 386) changed their prescribing practices including 32% (n = 154) who followed their patients more closely.

7% (n = 35) stopped treatment with SSRIs in at least one patient.

Physicians who had observed worsening depression/suicidality were more likely to discontinue treatment with SSRI's compared to those who had not observed these side effects previously (25% versus 6%, $p < 0.001$). (Cheung et al. 2008)



Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents

Robert D. Gibbons, Ph.D.

C. Hendricks Brown, Ph.D.

Kwan Hur, Ph.D.

Sue M. Marcus, Ph.D.

Dulal K. Bhaumik, Ph.D.

Joëlle A. Erkens, Pharm.D., Ph.D.

Ron M.C. Herings, Pharm.D., Ph.D.

J. John Mann, M.D.

Objective: In 2003 and 2004, U.S. and European regulators issued public health warnings about a possible association between antidepressants and suicidal thinking and behavior. The authors assessed whether these warnings discouraged use of antidepressants in children and adolescents and whether they led to increases in suicide rates as a result of untreated depression.

Method: The authors examined U.S. and Dutch data on prescription rates for selective serotonin reuptake inhibitors (SSRIs) from 2003 to 2005 in children and adolescents (patients up to age 19), as well as suicide rates for children and adolescents, using available data (through 2004 in the United States and through 2005 in the Netherlands). They used Poisson regression analyses to determine the overall association between antidepressant prescription rates and suicide rates, adjusted for sex and age, during the periods preceding and immediately following the public health warnings.

Results: SSRI prescriptions for youths decreased by approximately 22% in both the United States and the Netherlands after the warnings were issued. In the Netherlands, the youth suicide rate increased by 49% between 2003 and 2005 and shows a significant inverse association with SSRI prescriptions. In the United States, youth suicide rates increased by 14% between 2003 and 2004, which is the largest year-to-year change in suicide rates in this population since the Centers for Disease Control and Prevention began systematically collecting suicide data in 1979.

Conclusions: In both the United States and the Netherlands, SSRI prescriptions for children and adolescents decreased after U.S. and European regulatory agencies issued warnings about a possible suicide risk with antidepressant use in pediatric patients, and these decreases were associated with increases in suicide rates in children and adolescents.

(Am J Psychiatry 2007; 164:1356–1363)





Gibbons et al. Verordnungen und Suizide in den USA 2002-2004

FIGURE 1. SSRI Prescription Rates in the United States, 2002–2005, Stratified by Age Group and Expressed as a Percentage of the 2003 Rate

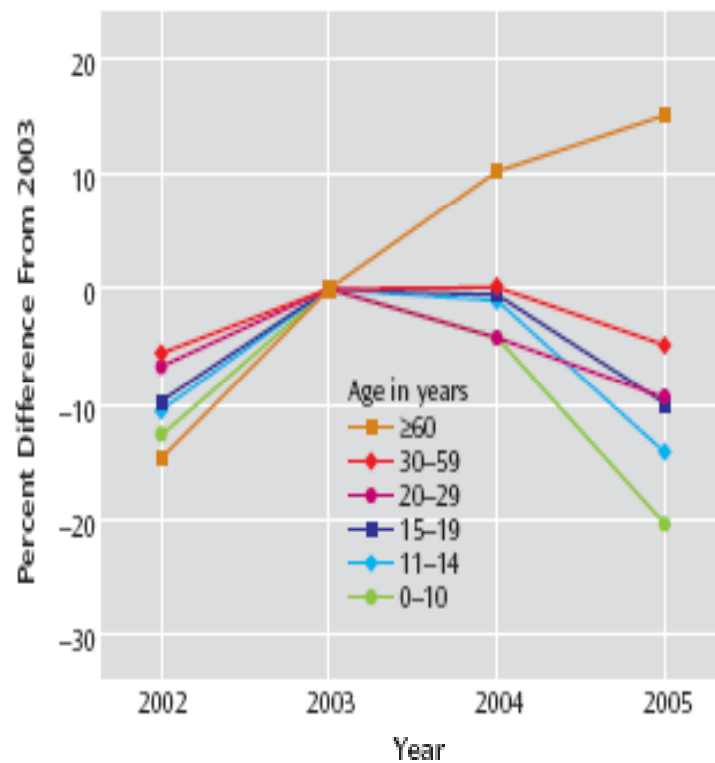
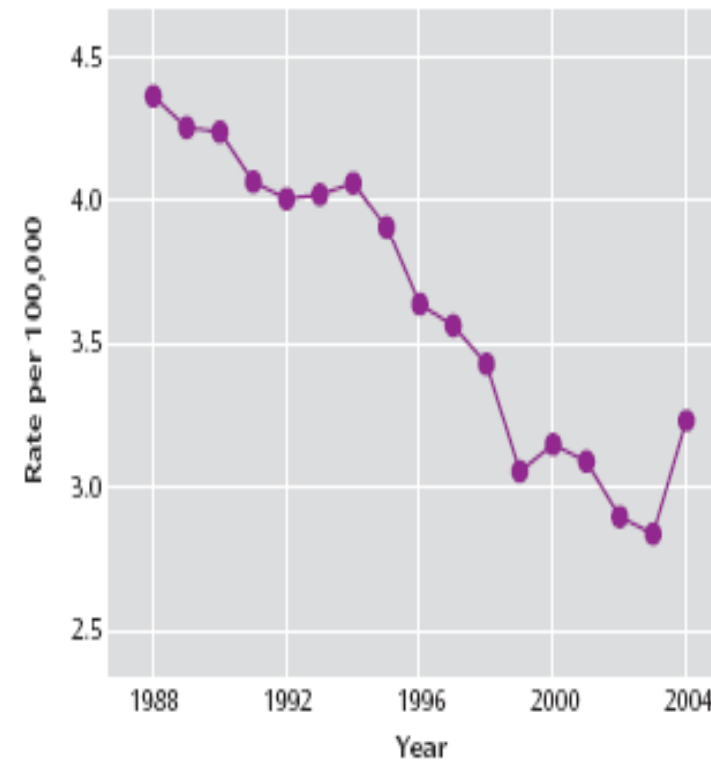


FIGURE 2. Suicide Rate in Children and Adolescents (Ages 5–19 Years) in the United States, 1988–2004





Diskussion in den USA

Suicide Trends Among Youths and Young Adults Aged 10–24 Years — United States, 1990–2004

PRESS CONTACT: National Center for Injury Prevention and Control
Media Relations (770) 488-4902

Study results show the largest increase in youth and young adult suicide rates in 15 years. The most noted change occurred in hanging/suffocation suicides among 10-14 year old girls.

(....)Between 1990 and 2003, the overall suicide rate for 10-24 year olds declined by 28 percent. **Between 2003 and 2004, however, the rate climbed by 8 percent, the largest single-year climb in 15 years.**

Copied MMRM sum. (<http://www.cdc.gov/od/oc/media/mmwrnews/2007/n070906.htm>)

 **MSNBC.com**

Newsweek

Teens and Antidepressants: Did Warnings Go Too Far?

Did an effort to reduce teen suicides backfire?

By Tony Dokoupil

Newsweek





Functional imaging, serotonin and the suicidal brain (Audenaert et al. 2006)

- ▶ Indirect research results include a reduced 5-HIAA in cerebrospinal fluid in violent suicide attempters
- ▶ Direct post-mortem research demonstrated an increase in 5-HT_{2A} receptors. Direct in vivo functional imaging with PET or SPECT demonstrated a reduction in 5-HT_{2A} binding index in suicide attempts in anxious and depressed suicide attempters and an increase in 5-HT_{2A} binding in impulsive suicide attempters.
- ▶ Interestingly, both an increase and a decrease in 5-HT_{2A} binding index seem to normalize with SSRI treatment.



Decreased frontal serotonin 5-HT 2a receptor binding index in deliberate self-harm patients. (Audenaert et al. 2001)

The reduction was more pronounced among deliberate self-injury patients (DSI) ($P < 0.001$) than among deliberate self-poisoning patients (DSP).

Frontal binding index was significantly lower in DSI patients than in DSP suicide attempters ($P < 0.001$).

It is concluded that brain SPET of the 5-HT_{2a} serotonin receptor system in attempted suicide patients who are free of drugs influencing the serotonergic system shows in vivo evidence of a decreased frontal binding index of the 5-HT_{2a} receptor, indicating a decrease in the number and/or in the binding affinity of 5-HT_{2a} receptors.



Postmortem Studien

- Älterer Bezugsrahmen (Henriksson et al 2001): Geringer Anteil der Suizidenten mit AD; 1/3 der Suizidenten hatte Spiegel von Psychopharmaka im Blut
- Neuerer Bezugsrahmen (Richa & Isacsson 1997): 2 fach höhere Rate von AD als früher; Rate Überdosis stabil, weniger Männer
- *most victims had not taken an antidepressant (most commonly SSRIs or other new generation antidepressants) immediately before their death, even though the majority had been depressed. Only 4% had toxic concentrations of antidepressants, meaning that the drugs were used in an intentional overdose.*
- Bericht der US Task force
- In a study of 49 adolescent suicides, a research team in Utah recently reported in an abstract that 24 percent had been prescribed antidepressants, but *none* tested positive for SSRIs at the time of their death (Gray et al, 2003).





Kein Hinweis auf besondere „Aggressivität“ der Methode

- **Suicides by Violent Means in Individuals Taking SSRIs and Other Antidepressants: A Postmortem Study in Sweden, 1992-2004, Fazel et al. 2007**
- The sample consisted of 14,691 suicides. Of the 1958 suicides with detectable levels of SSRIs, 1247 were by violent means (63.7%) compared with 7835 of 11,045 suicides (70.9%) in antidepressant-free group ($\chi^2_1 = 7.6$; $P < 0.01$).
- When subdivided by gender and age-bands, we found specific groups with significantly lower proportions of violent suicides compared with the antidepressants-free group, **including men aged 15-24 years.**



Zusammenhänge: depressive Jugendliche und Amoktäter?

- 1. Depressionen sind häufig ↔ Amoktaten sind selten**
- 2. Bei Amoktätern liegt eine vielgestaltige Psychopathologie zugrunde die nicht mit depressiven Störungen gleichgesetzt werden kann**
- 3. Es gibt eine Ähnlichkeit in manchen Symptomen (z.B. Sozialer Rückzug, Abkapselung, Lerngeschichte von Frustrationen)**
- 4. Der depressive Patient ist eher gehemmt, bei Amoktätern wird diese Hemmung durch Aggressionen durchbrochen**



Zusammenfassung

- Aktivierung ist ein Phänomen bei der Behandlung depressiver Patienten mit Antidepressiva
- Das Risiko für Suizidalität steigt bei jeder Behandlung zu Beginn
- Bisher gibt es keinen Hinweis, dass Suizide unter SSRI gehäuft sind bei Minderjährigen
- Post-mortem Untersuchungen geben bisher keinen Hinweis auf evt. Zusammenhänge
- Amoktaten sind bisher nicht ursächlich auf eine medikamentöse Behandlung zurück zu führen
- Bei der Behandlung entsprechender Patienten (narzisstische Grundpersönlichkeit, über eine reine Depression hinausgehende Psychopathologie) wird ein entsprechendes Monitoring sinnvoll und angemessen sein.



**Kinder- und Jugend-
psychiatrie / Psychotherapie**

Universitätsklinikum Ulm

- **Dr. Michael Kölch**

**Klinik für Kinder- und Jugendpsychiatrie /
Psychotherapie des Universitätsklinikums Ulm**

Steinhövelstraße 5
89075 Ulm

www.uniklinik-ulm.de/kjpp



Ärztlicher Direktor: Prof. Dr. Jörg M. Fegert

