Evolution of the WBC Monitoring Program for Clozapine

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Agenda

- Definitions
- Background
- Brief summary of July 1997 Psychopharmacological Drugs Advisory Committee (PDAC) meeting
- Data discussed at the June 2003 PDAC meeting
  - Key changes to WBC monitoring program in recently approved labeling

Definitions of blood dyscrasias as described in clozapine labeling

- Moderate leukopenia
  - 3000/mm3 > WBC ≥ 2000/mm3 and/or
  - 1500/mm3 > Absolute Neutrophil Count (ANC) ≥ 1000/mm3

- Severe leukopenia
  - WBC < 2000/mm3 and/or
  - ANC < 1000/mm3

- Agranulocytosis
  - ANC < 500/mm3
  - Clinical symptoms not required

Background

- The clinical development program for clozapine identified agranulocytosis (agran) as a serious adverse event associated with use of the drug occurring in 1-2% of patients
- Prior to FDA approval, European postmarketing data suggested a high fatality rate for agran associated with clozapine treatment (35%)
- FDA approved labeling required that the drug only be available through a distribution system that ensured weekly WBC monitoring ("NO BLOOD, NO DRUG")

Clozaril Patient Management System (CPMS)

- Sandoz's original conception of the WBC monitoring program at February 1990 product launch
  - Caremark was exclusive distributor and provider of weekly blood collection services
  - Roche Labs analyzed blood samples for WBC
  - Data on WBC counts and agran occurrence have been collected by the Clozaril National Registry (CNR)
  - Patients who developed severe leukopenia or agran are listed on the "non-rechallengeable list"

CPMS evolution

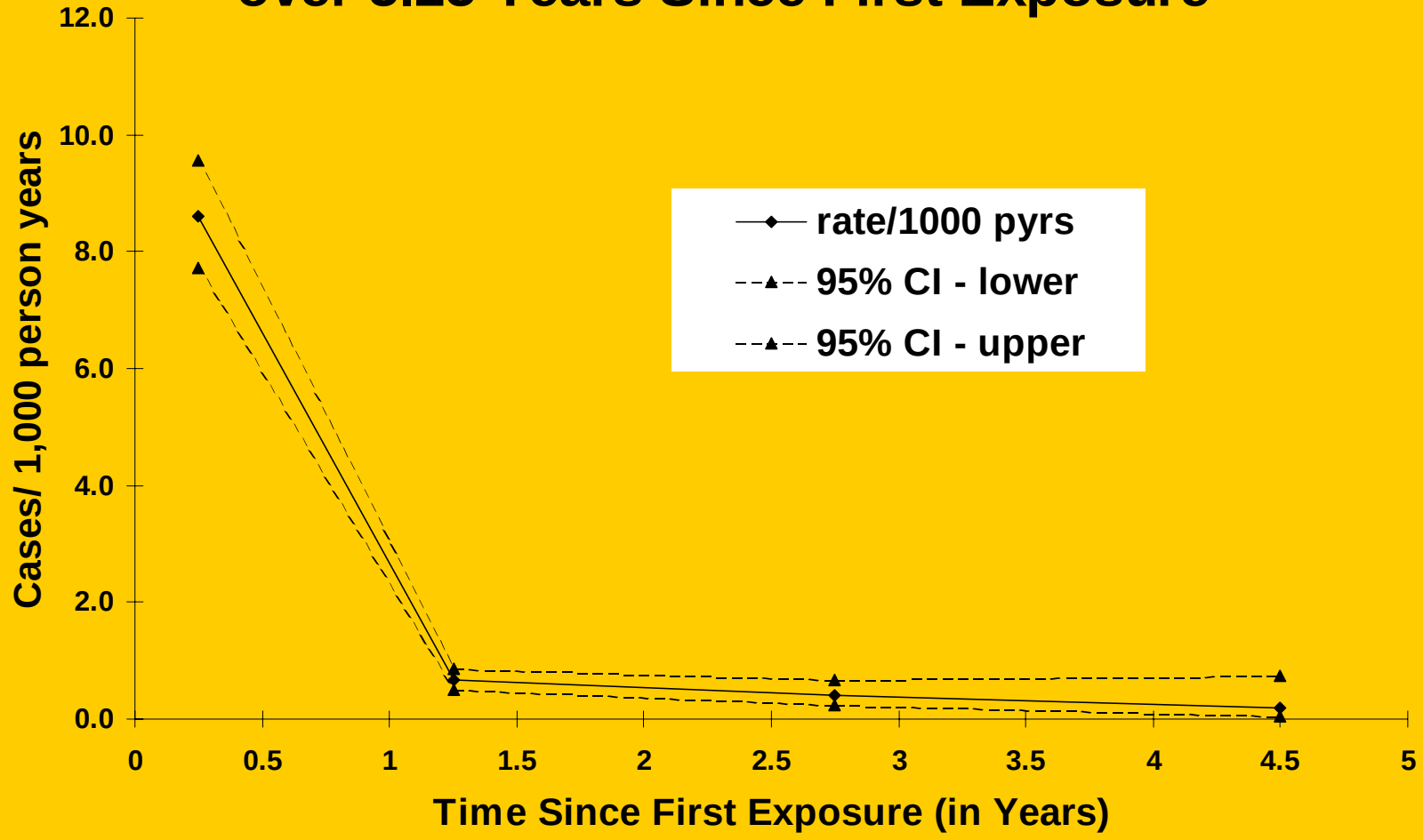
- VA, pharmacy groups, and others complained to FDA about the expense of clozapine only being available as part of the CPMS
- Sandoz was sued by 35 state attorneys generals for antitrust violations
- Conversion from CPMS to non-exclusive distribution occurred in May 1991
- Generic versions of clozapine must have a WBC monitoring program that is very similar to the innovator (became available in December 1997)
- All “non-rechallengeable” patients are maintained on one list by the Novartis

July 1997 PDAC meeting on WBC monitoring for clozapine

Questions for the July 1997 Clozaril Advisory Committee Meeting

- Should the frequency of WBC monitoring be reduced at some time point after initiation of therapy, and if so, when and what reduced frequency of WBC monitoring would be acceptable?
  - Should WBC monitoring stop altogether at some time point, and if so, when?
  - Should the program be changed overall, e.g.., should it become voluntary, as is most advice in labeling regarding monitoring for adverse events?

Rate of Agranulocytosis with Clozapine over 5.25 Years Since First Exposure



Recommendation of July 1997 PDAC meeting

- To allow decrease in monitoring to every 2 weeks after six months of weekly monitoring as long as WBC counts were stable
  - This change in the monitoring program was initiated April 1, 1998

Questions for the June 2003 Clozaril Advisory Committee Meeting

- Should the frequency of WBC monitoring be further reduced after some duration of every 2 week monitoring, and if so, when and what reduced frequency of WBC monitoring would be acceptable?
  - Should WBC monitoring stop altogether at some time point, and if so, when?
  - Should the program be changed overall, e.g.., should it become voluntary, as is most advice in labeling regarding monitoring for adverse events?
- Should the ANC be required as a part of WBC monitoring?

Rate of agranulocytosis by country and monitoring period

	Weeks 0-18 Rate (# of events)	Weeks 19-52 Rate (# of events)	Weeks >52 Rate (# of events)
Australian Data			
Agranulocytosis {per 1,000 pt. yrs. (N)}	8.3 (26) weekly	2.2 (11) monthly	0.5 (14) monthly
United Kingdom Data			
Pre-1995 (monitoring frequency)	24.8 (43) weekly	1.2 (3) Every 2 weeks	0.3 (2) Every 2 weeks
Post-1995 (monitoring frequency)	20.4 (119) weekly	1.5 (13) Every 2 weeks	0.6 (18) monthly
United States Data			
Pre-1998 (monitoring frequency)	8.8 (366) weekly	0.8 (50) weekly	0.4 (101) weekly
Post-1998 (monitoring frequency)	3.8 (40) weekly	1.0 (14) weekly/ Every 2 weeks	0.1 (2) Every 2 weeks

Recommendations of the 2003 PDAC

- The frequency of WBC monitoring could be decreased to every 4 weeks following some period of every 2 week monitoring (after 12-24 mos of therapy)
  - The change should be made only for patients who have had consistently normal WBC counts
  - They recognized that despite recommending the less frequent monitoring that the agran rate would likely increase as a result of this change
- The program should not be stopped and should not be made voluntary
- Absolute neutrophil count should be required with each WBC count and used as an independent criterion for moderate leukopenia and agran

Pertinent labeling changes based on PDAC analyses

- Reduction in the WBC/ANC monitoring frequency to every 4 weeks after 6 months of weekly monitoring and 6 months of every 2 week monitoring if there has been no interruption in therapy due to low WBC or ANC and WBC ≥ 3500/mm3 and ANC ≥ 2000/mm3.

- Requirement that the ANC be determined and reported along with each WBC count.
- Initiation of clozapine treatment only if WBC ≥ 3500/mm3 and ANC ≥ 2000/mm3.
- Addition of a low ANC criteria (<1500/mm3) for moderate leukopenia; i.e., if a patient has an ANC <1500/mm3 with a normal total WBC count, they qualify as having moderate leukopenia

Analyses conducted subsequent to the June 2003 PDAC meeting

- 7-15% of patients have a subsequent episode of granulopoietic dysfunction following an initial episode of moderate leukopenia
- The subset of patients who had at least one episode of moderate leucopenia had a rate of subsequent agran 3-10x higher than the full cohort

Rates of Severe Leukopenia and Agran Stratified by Number of Episodes of Moderate Leukopenia per 1000 person-years

Number of Episodes of ML	Number of Patients	Severe Leukopenia	Agran
1	2294	1.7	2.3
2	166	66.0	27.0
3	50	56.1	18.3
4 or more	64	76.0	20.6

Increased risk persists for about one year following recovery from original episode

Pertinent labeling changes based on these analyses

- Addition of cautionary language to prescribers describing the increased risk of agranulocytosis in patients who are rechallenged with clozapine following recovery from an initial episode of moderate leukopenia
- Requirement that patients who recover from moderate leukopenia (3000/mm3 > WBC ≥ 2000/mm3 and/or 1500/mm3 >ANC ≥ 1000/mm3) undergo weekly monitoring for 12 months if re-challenged.

Future challenges

- Educating prescribers and patients about the changes in the WBC monitoring program
- Assessing the effect of these changes on the agran rate
  - Lessening the frequency of monitoring for long-term users may increase risk of agran
  - Increasing frequency of monitoring for patients who've had an initial episode of moderate leukopenia may decrease risk of agran

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