How should clinicians and patients choose antihyperglycemic agents?

An evidence-based approach

Victor M. Montori¹, James Deming², Nilay D. Shah¹

¹ Knowledge and Evaluation Research Unit, Division of Diabetes and Endocrinology, and Division of Health Care and Policy Research, Mayo Clinic, Rochester, Minnesota, United States
² Diabetes Quality Initiative, Mayo Clinic Health System, Tomah, Wisconsin, United States

Correspondence to: Victor M. Montori, MD, MSc, Knowledge and Evaluation Research Unit, Division of Diabetes and Endocrinology, and Division of Health Care and Policy Research, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA, phone: +1-507-293-0175, fax: +1-507-538-0850, e-mail: montori.victor@mayo.edu

Received: May 12, 2011.
Revision accepted: May 13, 2011.
Conflict of interest: none declared.

Pol Arch Med Wewn. 2011; 121 (6): 208‑212
Copyright by Medycyna Praktyczna, Kraków 2011

KEY WORDS
antihyperglycemic agents, clinical decision making, patient-centered care, type 2 diabetes

ABSTRACT

The choice of antihyperglycemic agents has become more complex as new drug classes have appeared and evidence about their efficacy and safety accumulates. Unfortunately, direct and fair comparisons are lacking and the clinician and patient are left to decide among agents with different safety and burden profiles. Furthermore, the relative efficacy of these agents beyond their ability to lower hemoglobin A₁c — that is, in their ability to reduce the risk of diabetes complications — remains uncertain. In this sea of uncertainty, interests other than those of the patient actively shape choices. It is our expectation that better evidence, better policy and better decisions will eventually become routine in the care of patients with diabetes.

Antihyperglycemic agents in an evidence desert

In 2011, there is an ever-increasing range of antihyperglycemic options for the treatment of patients with type 2 diabetes. Agents from more than 10 drug classes cover a broad range of mechanisms thought to affect glycemia, including insulin release, insulin action, glucagon secretion, gut motility, carbohydrate absorption, and urinary glucose handling. This physiologic range and the fact that most patients require more than one agent to achieve glycemic goals invite the use of combinations. The result of multitude of choices challenges clinicians and their patients to ask: how shall we choose?

The choice of which antidiabetic agent to use in a given patient is one that could be very easy to answer if we had high-quality evidence comparing their short- and long-term effect on outcomes that matter to patients including benefits, harms, and inconveniences.

Alternatively, one could consider only the ability of these agents to reduce glycemia. As such it should then be expected that the benefits of glycemic control would follow the use of an effective antihyperglycemic agent. There are two problems with this alternative. The first one refers to the range of effects of antihyperglycemic treatments. The second one is the state of knowledge about the benefits of pharmacologically induced normoglycemia.

Until recently, effective glucose reduction — with sulfonylureas and insulin — was associated with increased risk of hypoglycemia. In this narrow sense, antihyperglycemic agents have always required careful use. Also, knowledge of this effect led to selective use of available agents: clinicians generally avoid long-acting sulfonylureas in patients at high risk of hypoglycemia, such as the elderly. Unfortunately, and this is a key concept in modern diabetology, the effects of therapeutic agents on glycemia do not fully capture their impact on patients, i.e., these agents have nonglycemic actions that cause important adverse effects, including mortality. Also, there appears to be no net benefit of pharmacologically aided normo- or near-normoglycemia in patients with type 2 diabetes using contemporary therapies.

This brings us back full circle: we need high-quality evidence comparing their short- and long-term effect on outcomes that matter.
to patients including benefits, harms, and inconveniences.

The latest evidence summary A recent systematic review of the available evidence comparing antihyperglycemic agents found that the available evidence was quite sparse, both for new and old agents, rarely assessed their impact on patient-important outcomes, and whatever evidence exists is fraught with imprecision and inconsistency. This is the best available evidence; an evidence-based approach must make use of this science, along with available mechanistic knowledge, to find a medicine that best fits the biology of the specific patient.

Interestingly, the recent systematic review focused on deriving head-to-head conclusions for both monotherapy and for second-line agents. Due to the inclusion criteria requiring that more than one agent be compared (i.e., no placebo-controlled trials), inferences for newer agents — all of which were compared against placebo — are limited. In addition, the authors suggest that the length of typical trials were brief and thus, long-term outcomes could not be assessed. Nonetheless, this review concludes that metformin is the best first-line agent and all two-drug combinations were similarly effective at reducing hemoglobin A1c (HbA1c) levels. Overall, monotherapy typically reduces HbA1c by one percentage point, with greater reductions achieved proportional to the baseline HbA1c, i.e., higher HbA1c will be associated with larger HbA1c reductions (TABLE).

The nature of choosing antihyperglycemic agents Unfortunately, glycemic control is not the only or most important goal for most patients with diabetes, and the biology of the specific patient is not the only or most important context to consider in choosing a diabetes agent. We put forward that patients with diabetes value living their lives as healthy people, able to seek dreams, care for loved ones, and pursue challenges unhindered by symptoms or side effects, disease complications or treatment burdens. Thus, these goals — and their priority for each specific patient — must be considered in choosing a diabetes drug.

One important aspect of these medicines is their cost to the user. In the United States, the out-of-pocket costs for the patient for these medicines can range from 5 cents per day to 10 dollars per day, making cost an important determinant of which agent to use. Newer agents and those not yet available in generic form are most expensive. Most newer agents (glitazones, glitazones [dipeptidyl peptidase 4 inhibitors] and other incretins such as glucagon-like peptide 1 [GLP-1] analogues) lower glucose in a glucose-sensitive way, i.e., they are associated with a negligible risk of hypoglycemia (and thus require minimal glucose monitoring), something they share with biguanides (metformin) and α-glucosidase inhibitors, two older drug classes. Weight loss is most common with injectable GLP-1 analogues; gliptins and metformin are weight neutral; glitazones and sulfonylureas lead to weight gain. Additional considerations include the need to self-monitor glucose and how they are used (route and frequency of dosing). There appears to be small differences in the extent to which these agents lower HbA1c (most powerful [HbA1c reductions in the 1%–2% range] appear to be metformin, sulfonylureas, and glitazones; insulin is by far the most powerful glucose-lowering agent).

In addition to these considerations, clinicians need to keep up to date with revelations of long-term consequences of these agents.

1 Metformin has accumulated some evidence suggesting that it may have beneficial cardiovascular and anticancer effects. That this agent can cause lactic acidosis is poorly supported by indirect and weak evidence. In patients with renal function impairment, caution often calls for restricting the use of metformin, but the threshold for discontinuation requires careful consideration of the remote yet potential risk of lactic acidosis against the disadvantages of the alternatives. Its main side effects appear to be gastrointestinal and, often, short-lived.

2 For some time, uncertainty existed about the cardiovascular effects of sulfonylureas. There

<table>
<thead>
<tr>
<th>Drug A</th>
<th>Drug B</th>
<th>Decrease in HbA1c</th>
<th>Weight gain</th>
<th>Likelihood of hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met</td>
<td>SU</td>
<td>A = B</td>
<td>A &lt; B</td>
<td>A &lt; B</td>
</tr>
<tr>
<td>Met</td>
<td>TZD</td>
<td>A = B</td>
<td>A &lt; B</td>
<td>NA</td>
</tr>
<tr>
<td>Met</td>
<td>DPP-4</td>
<td>A &gt; B</td>
<td>A &lt; B</td>
<td>NA</td>
</tr>
<tr>
<td>Met</td>
<td>Meg</td>
<td>NA</td>
<td>NA</td>
<td>A &lt; B</td>
</tr>
<tr>
<td>SU</td>
<td>Meg</td>
<td>A = B</td>
<td>A = B</td>
<td>A = B</td>
</tr>
<tr>
<td>SU</td>
<td>TZD</td>
<td>A = B</td>
<td>A &lt; B</td>
<td>A &gt; B</td>
</tr>
<tr>
<td>SU</td>
<td>GLP-1</td>
<td>NA</td>
<td>A &gt; B</td>
<td>A &lt; B</td>
</tr>
</tbody>
</table>

Abbreviations: DPP-4 — dipeptidyl peptidase 4 inhibitors (e.g., sitagliptin, saxagliptin), GLP-1 — glucagon-like peptide 1 analogues (e.g., exenatide, liraglutide), HbA1c — hemoglobin A1c, Meg — meglitinide (e.g., repaglinide, nateglinide), Met — metformin, NA — not available/applicable, SU — sulfonylureas (e.g., glipizide, glyburide, glimepiride), TZD — thiazolidinediones (e.g., pioglitazone, rosiglitazone).
The careful prescriber should educate patients on the importance of glycemic control. Yet, these benefits either do not exist or are yet to be demonstrated.

3 In the last few years, the spotlight has been on glitazones. Both agents available in this drug class have been associated with an increased risk of heart failure. Also, they reduce bone mineral density and in at-risk patients, e.g., postmenopausal women, can increase the risk of fragility fractures. Rosiglitazone appears to increase the risk of myocardial infarction by about 40% (comparable but in opposite direction to the magnitude of risk reduction expected with high-dose statins). Pioglitazone may also increase the risk of bladder cancer.

4 Data is accumulating supporting the safety of incretins, while some concerns have recently emerged from data reported by clinicians to the Food and Drug Administration (FDA) about an increased risk of pancreatitis and pancreatic cancer with these agents.

5 The use of insulin glargine, common in patients with type 2 diabetes, has been controversially associated with an increased risk of cancer.

Pathophysiological explanations exist to support all these effects. When taken together, it is clear that: 1) patients are choosing between drugs with potentially important side effects of different impact; 2) to offset these adverse effects, important benefits must also result from their use, yet these benefits either do not exist or are yet to be demonstrated.

What should clinicians and patients do? It is difficult to argue for any other drug to be used as first line other than metformin. The main exception would be patients who are very hyperglycemic when first diagnosed. In these patients, insulin is most effective and fast in improving symptoms and achieving glycemic control. But not all patients will place a higher value on fast improvements while placing a relatively lower value on using injectable agents, self-monitoring, and experiencing hypoglycemia even for short periods; for these patients metformin alone or with sulfonylureas is usually sufficient (alongside lifestyle modifications). While there are contraindications to the use of metformin, most are only weakly supported by evidence of harm, and some have been superseded as weak evidence of benefit has emerged (e.g., patients with heart failure).

We believe the patient should choose what agent to add to metformin after they begin experiencing hyperglycemia on metformin or with what to replace metformin if the patient cannot tolerate the drug. Here the distinct safety and burden profile of each of the available agents as we described above calls for patients and clinicians to consider these effects and choose which medicine best fits the patient's context. The careful prescriber should educate patients about the relatively high frequency with which new drugs are ultimately associated with previously unrecognized adverse consequences. Also, prescribers must be candid about their own preferences for these agents, as many may prefer to expose patients to new oral agents of relatively low potency rather than to embark with the patient on initiating insulin.

We have worked to develop interventions for use at the point-of-care that help clinicians and patients consider what is known about diabetes medicines and choose them based on the way they could affect issues patients consider important.

The alternatives to patient-centered approaches are formulary policies and clinical algorithms. Indeed, the American Diabetes Association and the European Association for the Study of Diabetes have proposed an algorithm that guides clinicians in choosing the ideal drug and drug sequence for most patients. According to this algorithm, all patients without contraindications must start with metformin, with sulfonylureas and glitazones as second-line agents, and incretins as third-line agents. The guidelines recommend initiating insulin as second-line agent among individuals with a HbA1c > 8.5% or hyperglycemic symptoms. However, given the impact of initiating insulin on the patient's life, this decision needs to be thoughtfully and jointly considered by the patient and the clinician.

The reality and our hope An analysis of prescriptions written for diabetes drugs in the last few years in the United States shows that rather than a practice-inspired by algorithms or based on patient preferences, the practice appears to reflect the adoption of the latest drugs or drug combinations. This appears particularly problematic given our discussion above of the lack of evidence of safety or efficacy of many of these preparations.

Much discussion comes from the literature. But this literature, we have uncovered, is in great part determined by the financial relationships the authors of published opinions have with for-profit interests. Wang et al. reported a very strong relationship between financial relationships and the direction of opinions about the safety of rosiglitazone and recommendations for its use.
continued use. These opinions likely delayed the removal of rosiglitazone from the European market and successfully kept this agent available in Canada and the United States. Similar financial interests appear to affect other aspects of diabetes care, including definition changes, target choices ("HbA1c < 7% by 2007"), and extant guidelines.

Large geographic variations also suggest that pharmaceutical detailing, lobbying, and deal-making with formulary administrations and other mechanisms are influencing prescription. Note that after the European removal of rosiglitazone from the market and the FDA restrictions in its use, Americans were still being actively prescribed this drug. In 2010, there were more than 2.5 million prescriptions filled for rosiglitazone in the United States. Prior to that we had observed significant geographical variation in use of these agents. This suggests the role of forces other than clinical needs of the patient.

Finally, experts often feel they have to use the latest agents to both accrue experience with these agents and to impress their patients into thinking they are keeping up-to-date. The only fair way we see to justify this practice is that these clinician preferences are explicitly shared with patients, that the experience is accrued as part of a formal protocol, and that these clinicians retain an instinctive skepticism about marketing claims that may be pushing them to adopt new agents faster than what their wisdom would recommend.

Thus, we have expectations for impartial regulatory agencies less interested in promoting innovation than in promoting safety; for formulary designers less interested in making deals than in ensuring that the pharmacopedia remains conservative; for clinicians who prescribe drugs conservatively and thoughtfully; and for informed and engaged patients who will actively participate in choosing the best antihyperglycemic drug for their specific context. To the extent that these actors work for patients’ well being, we see our expectations eventually satisfied. To the extent that health care delivery is seen as a profitable industry, our only hope will be a patient revolution.

REFERENCES

Jak lekarze i pacjenci powinni wybierać leki przeciwcukrzycowe?

Podejście oparte na danych naukowych

Victor M. Montori, James Deming, Nilay D. Shah

1 Knowledge and Evaluation Research Unit, Division of Diabetes and Endocrinology, and Division of Health Care and Policy Research, Mayo Clinic, Rochester, Minnesota, Stany Zjednoczone
2 Diabetes Quality Initiative, Mayo Clinic Health System, Tomah, Wisconsin, Stany Zjednoczone

Adres do korespondencji:
Victor M. Montori, MD, MSc,
Knowledge and Evaluation Research Unit, Division of Diabetes and Endocrinology, and Division of Health Care and Policy Research, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA,
tel.: +1‑507‑293‑0175,
fax: +1‑507‑538‑0850,
e‑mail: montori.victor@mayo.edu

Praca wpłynęła: 12.05.2011.
Przyjęta do druku: 13.05.2011.
Nie zgłoszono sprzeczności interesów.

STRESZCZENIE

Wybór leków hipoglikemizujących stał się obecnie bardziej złożony niż dotychczas, gdyż pojawiły się nowe klasy leków oraz mamy coraz więcej danych na temat ich skuteczności i bezpieczeństwa. Niestety brak jest bezpośrednich i bezstronnych porównań tych leków i lekarze oraz pacjenci stoją wobec wyboru spośród leków różniących się profilem bezpieczeństwa i obciążeń. Ponadto nadal brakuje pewnych danych odnośnie do ich względnej skuteczności, w tym zdolności do zmniejszania ryzyka rozwoju powikłań cukrzycy, a nie tylko zdolności do zmniejszania odsetka hemoglobin A$_{1c}$. Ponadto istotny wpływ na wybór leków mają interesy podmiotów innych niż pacjenci. Mamy nadzieję i oczekujemy, że lepsze dane naukowe, lepsza polityka oraz lepsze decyzje będą podstawą codziennej opieki nad pacjentami z cukrzycą.
Erratum


“Conflict of interest: none declared” on page 164 should have read “Conflict of interest: P. Jankowski has received fees and honoraria or funding for lectures, expert panel participation, articles, consultations, conference attendance, and research grants from Astra-Zeneca, MSD, Pfizer, Sandoz, and Sanofi-Aventis. He has also been the organizer of scientific events sponsored, among others, by Abbott, Astra-Zeneca, MSD, Pfizer, and Sanofi-Aventis.”

“Nie zgłoszono sprzeczności interesów” on page 171 should have read: “Zgłoszono sprzeczność interesów: P. Jankowski otrzymywał honoraria za wykłady, udział w panelach ekspertów, artykuły, konsultacje, udział w konferencjach, a także granty od firm Astra-Zeneca, MSD, Pfizer, Sandoz i Sanofi-Aventis. Organizował także spotkania naukowe sponsorowane m. in. przez firmę Abbott, Astra-Zeneca, MSD, Pfizer i Sanofi-Aventis.”
The premier European Event in internal medicine featuring:

- A high-quality scientific program covering all contemporary key aspects of internal medicine and related fields
- Outstanding international speakers presenting cutting edge scientific findings as they relate to clinical practice

Thematic streams include:

- Diabetes/Obesity
- Cardiovascular Diseases
- Infectious Diseases/Treatment of Chronic Viral Diseases/Hepatitis

Round Tables, Symposia, Debates:

- Resistance to Medicine
- Professionalism in Europe: 9 years later
- Metabolic syndrome and residual risk
- Clinical Focus in Antithrombotic Therapy
- Antiphospholipid Syndrome: Current Aspects
- and many more...

Highlights:

- Interactive sessions and networking opportunities bringing together experts of the laboratory research with clinical practitioners
- Book of abstracts published as a supplement in the European Journal of Internal Medicine

Organised by:

European Federation of Internal Medicine

Hosted by:

Hellenic Society of Internal Medicine

The 10th EFIM Congress is organized jointly with the 17th Congress of the Hellenic Society of Internal Medicine - HSIM

Take the EFIM web survey for internal medicine healthcare professionals!

Learn more @ www.efim2011.org

Deadline for abstract submission: June 30, 2011

Deadline for early registration: July 20, 2011

www.efim2011.org

efim2011@candc-group.com

Professional Congress Organiser:

C&C International Group of Companies

E. efim2011@candc-group.com
T. +30 210 68 89 130
F. +30 210 68 44 777

www.efim2011.org
1A, Pireas Str, 144 51, Metamorfosi, Athens Greece

EACCME accreditation details coming soon

Association Management
Professional Congress Organiser
Events & Destination Management
Strategy & Communication

MEMBERS OF
IAPCO

Certified by ISO 9001:2008
Serdecznie zapraszamy do udziału w Sympozjum „Nauka w służbie społeczeństwa – śladami Marii Skłodowskiej-Curie” „Science as public duty – following the ideas and work of Maria Skłodowska-Curie” będącego sympozjum satelitarnym 14. Światowego Kongresu Badań Radiacyjnych.

Organizatorami Sympozjum są:
Sekcja Chorób Serca u Kobiet Polskiego Towarzystwa Kardiologicznego,
Uniwersytet Jagielloński Collegium Medicum,
Polskie Towarzystwo Badań Radiacyjnych.

Sympozjum satelitarne odbywać się będzie w Collegium Medicum Uniwersytetu Jagiellońskiego w Krakowie w dniach 02–03.09.2011.

**Future directions in cardiovascular research – would they impact diagnostics in women?**
Chairmen: Prof. Danuta Czarnecka, Prof. Waldemar Banasiak, Prof. Kalina Kawecka-Jaszcz
Prof. Renata Cifkova (Czech Republic), Epidemiology and prevention of cardiovascular diseases.
Prof. Serap Erdine (Turkey), Gender differences in pathophysiology and treatment of hypertension.
Prof. Barbara Jarząb (Poland), New techniques in diagnostic imaging – PET-CT for imaging of cardiovascular disease.
Prof. Witold Rużyłło (Poland), New techniques in diagnostic imaging – cardiology.
Prof. Zdzisława Komacewicz-Jach (Poland), Interventional cardiology in women – are complications in 2011 still an important problem?
Prof. Kalina Kawecka-Jaszcz (Poland), Treatment of oncologic patients with heart disease.
Prof. Krzysztof Krzemieniecki (Poland), Cardiologic complications among women undergoing oncologic treatment.
Prof. Beata Tobiasz-Adamczyk (Poland), Health related quality of life in women after cancer treatment.

**Social and cultural determinants of women health**
Chairmen: Prof. Beata Tobiasz-Adamczyk, Prof. Sara Carmel
Prof. Mall Leinsalu (Sweden), Epidemiological evaluation of gender-related differences in health.
Prof. Sara Arber (England), Gender-related differences in quality of sleep.
Prof. Sara Carmel (Israel), Gender and will to live in older age.
Prof. Antonina Ostrowska (Poland), Gender-related inequalities in health.
Prof. Krystyna Slany (Poland), Gender-related inequalities in Poland.
Prof. Małgorzata Fuszara (Poland), Developement of gender studies in Poland.

Udział w sympozjum jest bezpłatny i gwarantuje punkty edukacyjne.
Gdy klikniesz uzyskasz dostęp do programu eMPendium, który pozwala Ci korzystać z elektronicznych wersji najważniejszych podręczników Medycyny Praktycznej, artykułów publikowanych w naszych czasopismach, Indeksu leków MP oraz modułu Gabinet, usprawniającego pracę gabinetu lekarskiego i przychodni.

Połączenie między poszczególnymi modułami zapewnia wyszukiwarka, która umożliwia przeszukiwanie treści wszystkich książek, artykułów z czasopism oraz Indeksu leków, z uwzględnieniem zdefiniowanych słów kluczowych i ich synonimów. Dzięki temu uzyskasz wyczerpujące informacje na niemal każdy temat związany z medycyną.

**Podręczniki**


Treść elektronicznych wersji podręczników jest na bieżąco aktualizowana.

Każdy podręcznik zawiera ryciny, tabele oraz filmy. Nowością w wersji elektronicznej podręcznika „Choroby wewnętrzne” są bogato ilustrowane atlasy: hematologiczny, badań obrazowych klatki piersiowej i in.

**Czasopisma**

Moduł zapewnia dostęp do artykułów publikowanych na łamach wszystkich czasopism Medycyny Praktycznej, pozwalając na interaktywne korzystanie z ich treści, np. szybkie wyszukiwanie, dodawanie własnych notatek do treści artykułu czy zakreślanie fragmentów tekstu.

**Leki**

Moduł ten zawiera aktualizowany bieżąco system informacji o lekach opracowany przez zespół redakcyjny Medycyny Praktycznej. Baza leków dynamicznie zmienia swoją zawartość, a codziennie aktualizowanych jest kilkudziesiąt rekordów. Korzystając z danych zawartych w module Leki, można drukować recepty w ramach modułu Gabinet.

**Gabinet**

Moduł do obsługi gabinetu lekarskiego lub przychodni, który znacząco usprawnia prowadzenie dokumentacji medycznej.

W skład tego modułu wchodzą: wyszukiwarka, terminarz, wielofunkcyjna elektroniczna kartoteka pacjentów; umożliwia drukowanie recept, zaleceń dla pacjenta, skierowań, zaświadczeń i zleceń oraz wystawianie druków ZUS ZLA, rachunków i faktur.

eMPendium dostępne jest w wersjach na komputery PC z systemem Windows, tablety z systemem Android, iPad oraz telefony komórkowe (iPhone, Android, Symbian, Windows Phone 7)

www.empendium.mp.pl